RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK

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I hereby declare that the thesis entitled "**RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK**" submitted towards partial fulfillment of the requirements for the award of **MD in Critical Care Medicine** degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Parshotam Lal Gautam**, Professor & Head, Department of Critical Care Medicine, **Dr. Bishav Mohan**, Professor, Department of Cardiology and **Dr. Gunchan Paul**, Associate Professor, Department of Critical Care Medicine. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

my Family,

friends

&

Teachers

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DR. JEEVAN KUMAR

ABBREVIATIONS

ABG	Arterial Blood Gas
ACCP	American College of Chest Physicians
AKI	Acute Kidney Injury
BMI	Body Mass Index
CO_2	Carbon Dioxide
CVP	Central Venous Pressure
DAMP	Danger-Associated Molecular Patterns
EDA	End Diastolic Area
EGDT	Early Goal Directed Therapy
FAC	Functional Area Change
GCS	Glasgow Coma Score
HR	Heart Rate
ICU	Intensive Care Unit
IFN	Interferon
IL	Interleukin
IV	Intravenous
IVC	Inferior Vena Cava
LV	Left Ventricle
LVEDA	Left Ventricular End Diastolic Area
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVEF	Left ventricular ejection fraction
LVESA	Left Ventricular End Systolic Area
LVESV	Left Ventricular End Systolic Volume
MAP	Mean Arterial Pressure
NF-kb	Cytosolic Nuclear Factor-kb
OHS	Obesity Hypoventilation Syndrome
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PAMP	Pathogen-Associated Molecular Patterns
PASP	Pulmonary Arterial Systolic Pressure
PMNs	Polymorphonuclear Leukocytes
PRRs	Pattern Recognition Receptors

PVR	Pulmonary Vascular Resistance
qSOFA	quick Sequential Organ Failure Assessment
RV	Right Ventricle
RVEDA	Right Ventricular End Diastolic Area
RVEF	Right Ventricular Ejection Fraction
RVESA	Right Ventricular End Systolic Area
SCCM	Society of Critical Care Medicine
SCM	Septic cardiomyopathy
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
SvO2	Mixed Venous Oxygen Saturation
TAPSE	Tricuspid annular plane systolic excursion
TAPSE	Tricuspid annular plane systolic excursion - TAPSE (mm),
TLR	Toll like Receptor
TNF	Tumor Necrosis Factor
TRmax	Tricuspid Regurgitation velocity
TTE	Trans Thoracic Echocardiography
WBC	White Blood Cell

ABSTRACT

BACKGROUND: Sepsis related cardiomyopathy is a well-established entity now. The right ventricle (RV) usually takes a backseat both in literature and bedside when compared to left ventricle (LV). There is need for defining, analysing and mapping RV dysfunction in septic shock.

AIMS AND OBJECTIVES: To find the incidence of RV dysfunction in septic shock and to correlate RV dysfunction with outcomes of septic shock like Acute Kidney Injury (AKI), Respiratory failure and Mortality.

MATERIALS AND METHODS: We assessed echocardiographic parameters in critically ill patients admitted with septic shock. We defined RV dysfunction as fractional area change (FAC) less than 35% or tricuspid annulus systolic plane excursion (TAPSE) less than 16mm or RV dilatation (RVEDA/LVEDA >0.6) with RA pressures > 8mmhg. Using multivariate regression, we assessed the relationship between 28-day mortality, AKI with RV dysfunction and LV systolic dysfunction.

RESULTS: The study included 100 patients. Both RV and LV dysfunction were common (55% and 42%, respectively). Mean echocardiographic values were: RV end-diastolic area - 22.22 $\pm$ 4.61 cm^2, RV end-systolic area - 3.8 $\pm$ 3.31cm^2 ,RV FAC - 37.49 $\pm$ 9.9 % , TAPSE - 19.09$\pm$5.01 mm , LV EF - 46.99 $\pm$ 14.07 %. Patients with RV dysfunction had higher 28-day mortality (47.3% vs 27.3%, P – 0.035) and higher AKI (72.7% vs 42.4 %, P – 0.007). The multivariable regression analysis, RV dysfunction was associated with increased mortality (OR, 3.847; CI 95%; P- 0.047), and AKI (OR, 2.946; CI 95%; P-0.03)

CONCLUSION: RV dysfunction is common in septic shock and it is associated with poor outcomes like Acute kidney injury and mortality.

KEYWORDS: Right ventricular dysfunction, septic shock, septic cardiomyopathy, sepsis.

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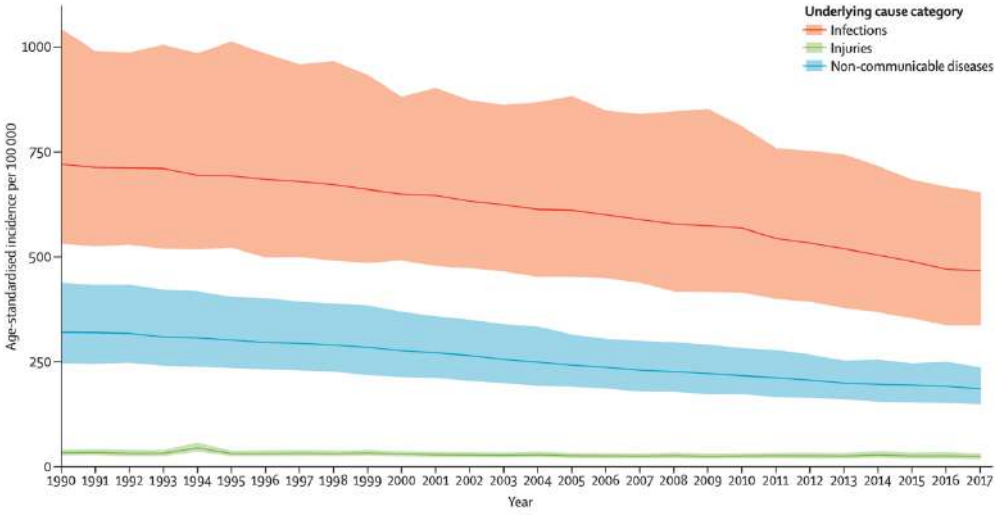
INTRODUCTION

Sepsis is a significant critical care disease with exceedingly high mortality. In the global report on the epidemiology and burden of sepsis published in 2020[1], it was estimated that till 2017, 49 million individuals were affected by sepsis and approximately 11 million deaths worldwide were related to sepsis which were potentially preventable deaths. Sepsis is among the very few diseases affecting both the developed and developing parts of the world although the disease burden is relatively higher in middle- and low-income countries. Every hour, about 1,000 people and each day around 24,000 people die from sepsis worldwide.[2,3]

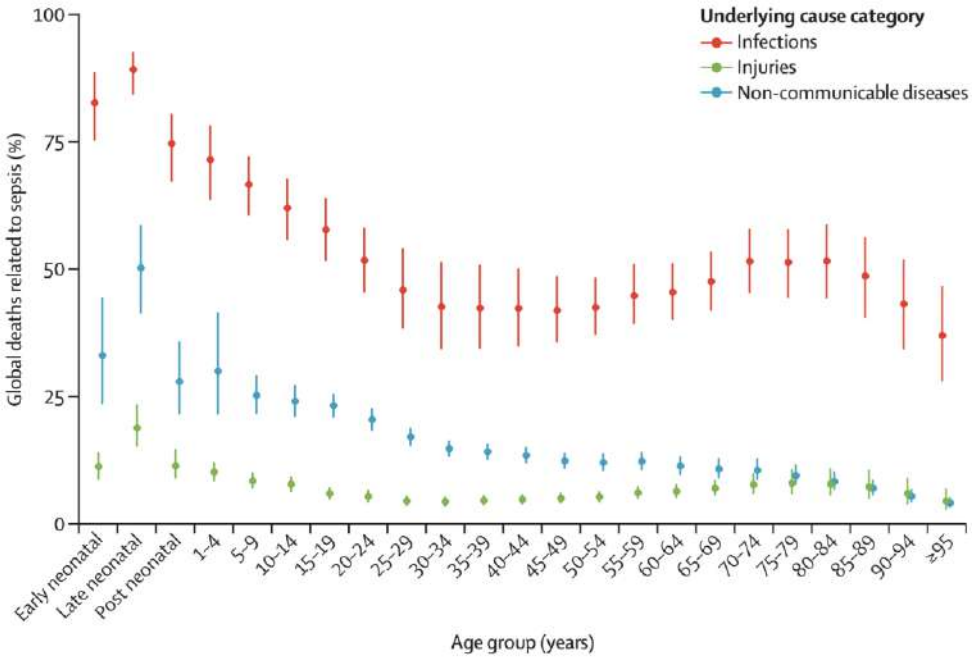
PICTURE 1: AGE-STANDARDISED GLOBAL SEPSIS INCIDENCE PER 100000 POPULATION, FOR BOTH SEXES AND BY UNDERLYING CAUSE CATEGORY, 1990–2017[3]



Despite accounting for such high mortality and morbidity, sepsis is one of the least understood entities.

Sepsis favorably affects vulnerable populations such as pregnant, patients of extreme age group, patients with underlying chronic comorbidities, and the immunocompromised. Rapidly emerging antimicrobial resistance further complicates the sepsis and adds significantly to the challenges and burden of the disease.

PICTURE 2: Percentage of all sepsis-related deaths in each underlying cause category, by age group and for both sexes, in 2017[3]



Different microorganisms have different virulence, but in overall sepsis is associated with substantial hospital mortality of 25%–30%.[4] Mortality rates in severe sepsis and septic shock have been decreasing owing to greater emphasis, awareness, clear guidelines, availability of antimicrobials and effective source control strategies. Nonetheless, the risk of death remains significantly high in comparison to other critically ill patients.

The management of sepsis has been the subject of interest and need for past few decades. There are periodically published international guidelines regarding optimum management of sepsis. At its core, the recommendations suggest early recognition of the disease, timely support of failing organs and swift control of the underlying infection. In the 2018 version of Surviving Sepsis Campaign guidelines[5], the previously practiced 3- and 6-hour bundles have been combined into a single “1-hour bundle”.

The guidelines recommend initiating fluid resuscitation of 30 ml/kg of crystalloids within 1 hour in septic shock and to complete it by 3 hours. This has not been changed in the 2021 surviving sepsis guidelines as

well.[6] If even after initial fluid resuscitation the mean arterial pressure (MAP) does not improve to about 65 mm Hg, then it is recommended that vasopressors be initiated.[6] An underlying cardiac dysfunction can complicate things with approach.

The risk of death in sepsis is largely dependent on disease severity, and it is related to the number of organs failing in the septic condition.[7] Circulatory compromise is a hallmark of severe sepsis, and even more so in septic shock. The clinical picture can be worsened further by the addition of cardiac dysfunction as a complication of sepsis. A septic organ dysfunction specifically affecting the heart known as septic cardiomyopathy has been identified.[8] The addition of septic cardiac dysfunction increases the risk of death in sepsis. Its characteristics and frequency, as well as its long-term consequences, are among the keenly studied aspects in the recent times.

Even from the introduction of septic cardiomyopathy, like it happens in everything related to the heart, the left ventricle has taken the front seat. Majority of prior studies have largely focused on left ventricular (LV) involvement in septic myocardiopathy. With the shift of focus on judicious fluid resuscitation, the adverse effects of fluid overload, venous congestion, and capillary leak in last decade, right ventricle also has found its way into the limelight of investigators. There has been greater recognition of right ventricular (RV) involvement in sepsis in the last few years and all aspects of RV similar to LV, are being studied for therapeutic and prognostic indications.

In endotoxemia and septic shock, the RV faces two obstacles, an increase in Pulmonary vascular resistance (PVR) due to increased plasma levels of endothelin-1 and proinflammatory cytokines such as interleukin 1-β, interleukin 6 and tumor necrosis factor α, and a decrease in contractility, as a part of septic cardiomyopathy.[9]

Sepsis is characterized by vasodilation and decreased resistance in systemic circulation, whereas the pulmonary vasculature resistance may increase due to hypoxic vasoconstriction, acute lung injury, hypercarbia, imbalance in endogenous vasodilators and vasoconstrictors, vascular microthrombi and the presence of

mechanical ventilation. Fluid administration in sepsis management, further increases the RV preload, which in the setting of elevated afterload compensates by further increasing end diastolic volume and pressure, leading to isolated RV dysfunction.[10] Lack of specific resuscitation strategies in RV dysfunction may lead to its failure. Furthermore, RV dysfunction is associated with false-positive fluid responsiveness, wherein changes in left ventricular outflow parameters or its surrogate with respiratory variation are used to determine fluid responsiveness.[11] In these patients, further fluid administration can lead to venous congestion, capillary leak and worsening of organ dysfunction.

There is a crucial need for understanding RV dysfunction in sepsis and the causative mechanisms associated with higher mortality in this population. This will significantly influence how we prevent and manage this disease process. Majority of the studies are undertaken in western parts of the world and echocardiographic findings were taken as part of post hoc analysis from different major studies. Thus, we propose to conduct a prospective study with the aim of finding incidence of RV dysfunction in sepsis and corelating it with outcomes in septic shock.

AIMS AND OBJECTIVES

Primary objective:

To find the incidence of RV dysfunction in septic shock.

Secondary objective:

To correlate RV dysfunction with outcomes of septic shock

- Acute Kidney Injury (AKI)
- Respiratory failure
- Mortality in septic shock.

REVIEW OF LITERATURE

Sepsis is a life-threatening complication in response to infection causing end-stage organ dysfunction and death. The word sepsis is derived from Greek term “sepo” which means “make rotten” or “decomposition”. The term was used as early as in Greek poet Homer’s works and first described by Hippocrates in 400 BC to describe the process through which infected wounds become purulent.[12]

MILESTONES IN INFECTIOUS DISEASES

1546 Germ theory of infections - Girolamo Fracastoro

1752 Antiseptic practices - John Pringle , a British army surgeon

1860 Joseph Lister used carbolic acid for asepsis.

1879 Streptococcus was identified as source of puerperal sepsis by Louis Pasteur.

1882 Robert Koch identified bacteria causing tuberculosis

1892 Endotoxin causing shock was identified by Richard Pfeiffer

1928 Alexander Fleming discovered Penicillin.

Although the term sepsis dated old, it took over more than 2000 years to understand the pathophysiology of sepsis. Hugo Schottmueller in 1914 tried to define sepsis and said that “sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms.[13]

During the course of 20th century many trials and experiments were conducted to understand sepsis and its mechanism. Given the heterogeneity of the disease process, no clear consensus could be made regarding recognition and management of sepsis. So the Schottmueller’s definition remained unchanged during the course of many decades. There was a need however to develop guidelines for recognition and management of sepsis that were acceptable and replicable globally. So multiple consensus have been formed over last 3 decades for this purpose.

Sepsis 1 - 1991[14]

The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) emphasised that sepsis was an 'ongoing process.' They introduced and categorised entities as Systemic inflammatory response syndrome (SIRS), Sepsis, Severe Sepsis, Septic Shock and Multiple Organ Dysfunction Syndrome. These were then used by the clinicians worldwide.

- **SIRS** - any two of
    1. Body temperature : > 38^{o} or < 36^{o} Celsius.
    2. Heart rate (HR) : > 90 beats/minute.
    3. Respiratory rate : > 20 breaths/minute or partial pressure of CO2 less than 32 mmHg.
    4. WBC Count : White blood cell count (WBC) >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms
- **Sepsis** - SIRS with suspected or confirmed sepsis.
- **Severe Sepsis** – Sepsis plus organ dysfunction
- **Septic Shock** – sepsis induced hypotension despite adequate fluid resuscitation with indicators of perfusion abnormality like, lactic acidosis, oliguria, altered mental status.

LACUNAS IN SEPSIS 1 DEFINITION [13]

SIRS response may be observed without infection and inflammation is a very non-specific response to any insult.

Sepsis is a complex interplay of pro-inflammatory and anti-inflammatory and can range from hyper-inflammation and hypo-inflammation.

Sepsis 2 - 2001[15]

SCCM, the ACCP, ESICM, the American Thoracic Society and the Surgical Infection Society met for the second consensus and updated the criteria for sepsis. Signs and symptoms of sepsis were expanded in numbers and detail. General parameters and parameters pertaining to inflammation , hemodynamics, organ dysfunction, tissue perfusion and

also biochemical markers were elaborated in detail. However the old diagnostic criteria for sepsis was retained.

Sepsis 3 - 2016[16]

The new definitions of sepsis and septic shock were given in the international consensus held in 2016, and the qSOFA (quick Sequential Organ Failure Assessment) scoring system was developed for the early identification of simultaneous organ dysfunction in sepsis.

QSOFA criteria:

Altered mental status (GCS score <15)

Systolic blood pressure <100 mm Hg

Respiratory rate >22 breaths per min

- **Sepsis** - A life-threatening organ dysfunction caused by dysregulated host response to infection.

  Clinical criteria for Sepsis - Suspected or documented infection and an acute increase of ≥ 2 Sequential Organ Failure Assessment (SOFA) points.
- **Septic Shock** - A subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.

  Clinical criteria for Septic shock - Sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP ≥65 mm Hg and lactate >2 mmol/L despite adequate fluid resuscitation.

PICTURE 3: SOFA score[17]

	1	2	3	4
Respiration PaO2 /FiO2 (mm Hg)	<100	<300	<200	<100
Coagulation Platelets x $10^3/mm^3$	<150	<100	<50	<20
Liver Bilirubin (mg/dl)	1.2- 1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	Map<70	Dopamine ≤5 or (any)	Dopamine >5 norepinephrine ≤0.1	Dopa >15 norepi > 0.1
Central nervous system Glasgow Coma Score	13-14	10-12	6-9	<6
Renal Creatinine(mg/dl) Urine output(ml)	1.2-1.9	2.0-3.4	3.5-4.9	>5.0

PATHOPHYSIOLOGY OF SEPSIS

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis causes a multifaceted disruption of the finely tuned immunological balance of inflammation and anti-inflammation.

Physiological Response To Infection[18,19]

The physiological host response to an infection commences when host immune cells, recognize and bind to structural components on the microbes. Three entities are involved in this process.

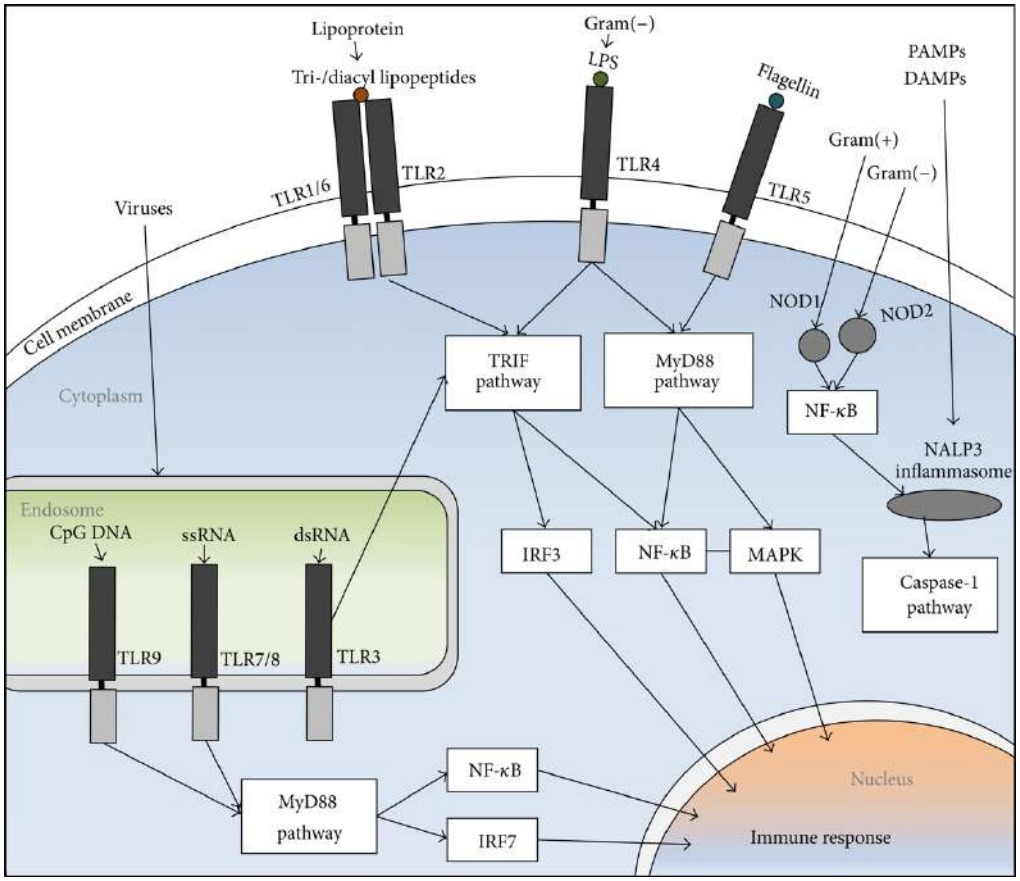
1. Pattern Recognition Receptors (PRRs) are expressed by immune cells which are activated by invading microorganisms. These include Toll-like receptors (TLRs), C-type lectins receptors, Nod-like receptors (NLRs), RIG-I like receptors and DNA sensors.

2. Pathogen-Associated Molecular Patterns (PAMPs) are expressed by the structural components of microbes. These include lipopolysaccharide (LPS) or lipoteichoic acid, peptidoglycans, lipopeptides, flagellin and bacterial DNA. PRRs recognise the PAMPs.
3. Danger-Associated Molecular Patterns (DAMPs) are present in the host which upon the microbial insult signal the PRRs to recognise to PAMPs. These include nucleosides, self-DNA (e.g. mitochondrial DNA), non-coding RNAs (e.g. micro-RNA), heat shock proteins, fibrinogen.

Distinct signaling pathways become activated leading to the activation of target genes including those encoding pro-inflammatory cytokines such as TNF, interleukin (IL)-6, IL-12 as well as interferons (IFNs) and can initiate a life-threatening **'CYTOKINE STORM'.**[20]

4. Fig. (1). Ligation of pathogen-associated molecular patterns (PAMPs) to their cognate pattern recognition receptors (Distinct signaling pathways become activated leading to the activation of target genes including those encoding pro-inflammatory cytokines such as TNF, interleukin (IL)-6, IL-12 as well as interferons (IFNs) and can initiate a life-threatening **'CYTOKINE STORM'.**

PICTURE 4: Schematic overview of TLR and NLR signalling pathways. PAMPs and DAMPs are recognized by PRRs.[21]



Polymorphonuclear leukocytes (PMNs) get activated and express adhesion molecules. The PMNs then go through rolling, adhesion, diapedesis, chemotaxis and migrate to the site of injury.

NETosis is developing neutrophil extracellular traps (NETs), consisting of modified chromatin decorated with bactericidal proteins. Many pathogens, antibodies and immune-complexes, cytokines, can cause NETosis.[22] This is a dynamic process involving proinflammatory, and anti-inflammatory mediators. A proinflammatory process is not followed by a compensatory anti-inflammatory phase. Rather, the two processes progress with a high degree of synchrony, albeit not necessarily with the same time course. But systemic immunosuppression typically dominates to some extent.[23]

The Complement system is activated by microbial components, contributing to the proinflammatory state.

Sepsis develops when there are proinflammatory mediators exceeding the normal response to an infection, leading to a generalized response leading to wide spread cellular injury. Mechanisms of the wide spread cellular injury include:

- Tissue Ischemia - Insufficient Oxygen Delivery,
- Cytopathic Injury - Direct Injury by Inflammatory Mediators
- Altered Rate of Apoptosis

Endothelial injury :

The proinflammatory state leads to vascular leakage. Activated endothelium also upregulates Nitric oxide(NO) resulting in vascular smooth muscle relaxation and systemic hypotension. Endothelial cell activation also plays an important role in the development of organ dysfunction and a procoagulant state leading to disseminated intravascular coagulation.

Organ dysfunction in Sepsis

Lung – Enhanced microvascular permeability leads to interstitial and alveolar pulmonary edema. PMNs entrapment within the lung's microcirculation leads to injury in the alveolocapillary membrane further leading to ventilation-perfusion mismatch and leads to hypoxemia. All this can lead to Acute respiratory distress syndrome.

Gastrointestinal tract – Altered gut's barrier function, causing translocation of bacteria and endotoxin into the systemic circulation and adding to septic response

Kidney - Acute tubular necrosis secondary to hypoperfusion and hypoxemia is one of the main mechanism of AKI in sepsis. However, Direct renal vasoconstriction, effect of cytokines and endotoxins also contribute to renal injury.

Nervous System- Altered sensorium is the most common manifestation of CNS in sepsis. Mechanisms are poorly understood.

Myocardial dysfunction in Sepsis

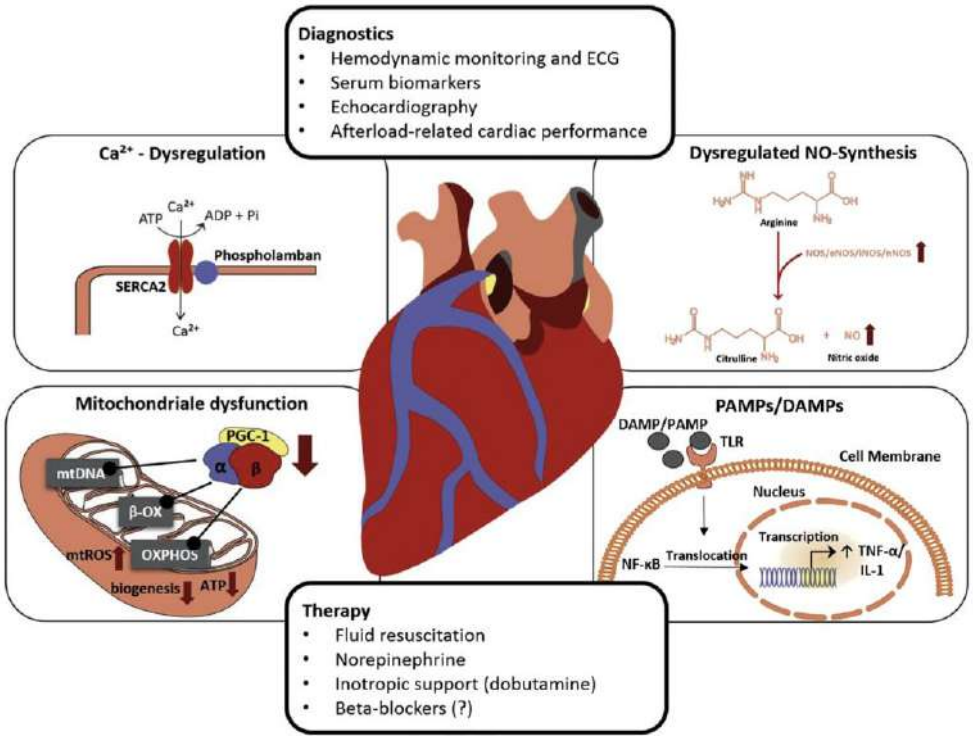
Cardiac dysfunction in sepsis, also known as “septic cardiomyopathy (SCM)” is common and associated with increased mortality.[24] SCM

was described in the early 1980s as an acutely reduction in left ventricular ejection fraction (LVEF). Now it includes both systolic and diastolic functions of right and left heart.[8] Research has identified cytokines.

Mitogen activated protein kinases, complement system, nitric oxide dysregulation, high-mobility group and lipopolysaccharide as potential causative agents for SCM. Increased cardiomyocyte oxidative stress is also associated with the development of SCM. When severe, SCM may contribute to a cascade of interdependent organ failure. Early studies of SCM pathophysiology focused primarily on systolic and diastolic dysfunction of the LV, but increasing attention to the right side has revealed that the RV may play an important and possibly independent role in SCM and its downstream effects.[25] While the RV has less muscle mass than the LV, the two ventricles are connected both in series and via a common septum leading to ventricular interdependence.[26] Under normal conditions, the RV matches the LV cardiac output to maintain left sided filling and forward flow. During sepsis, the combination of increased RV afterload, decreased RV filling with or without poor contractility may hamper the RV ability to keep up with the LV.[25]

Aggressive fluid resuscitation in the setting of RV dysfunction can lead to venous congestion, increased capillary pressures and lead to various other organ dysfunctions including AKI and pulmonary edema.

PICTURE 5: Pathophysiologic mechanisms and factors that cause a cardiac dysfunction associated with sepsis[27]



Surviving Sepsis Campaign (SCC)

In 2004, an international group of experts prepared guidelines that could be practiced bedside in the management of sepsis and septic shock and improve the outcomes.[28] These guidelines were updated in 2008[29] and 2012[30]. These versions of guidelines emphasised on a protocolized quantitative resuscitation called Early Goal Directed Therapy (EGDT) in these updates. The goals of first 6 hours being CVP 8–12 mm Hg, MAP ≥ 65 mm Hg, Urine output ≥ 0.5 mL/kg/hr and Superior vena cava oxygenation saturation (Scvo2) or mixed venous oxygen saturation (SvO2) 70% or 65%.

SCC-2016 subsequently removed EGDT from the guidelines in view of lack of mortality benefit in large trials and emphasised on fluid resuscitation of 30ml/kg in first 3 hours.[31] Bundled targets to be achieved within 3 hours and 6 hours were introduced.[32]

- The 3-hour bundle included a lactate level measurement; blood cultures and followed by intravenous (IV) broad-spectrum

antibiotics; and IV crystalloids at 30 mL/kg if hypotension or the lactates ≥ 4 mmol/L (36 mg/dL).

- The 6-hour bundle included remeasurement of lactate if it was initially raised; use of vasopressors if hypotension (MAP < 65 mmHg) persists despite fluid resuscitation. Use of central venous pressure (CVP) and central venous oxygen saturation (ScvO2) in cases of persistent hypotension despite volume resuscitation or the initial lactates ≥ 4 mmol/L

Later on the emphasis was given on treating the patients with sepsis and septic shock as a medical emergency requiring assessment and management on urgent basis. This led to the further modification of the SSC 2016 guidelines with an update in 2018 which clubbed the 3 and 6 hour bundle into 1 hour bundle.[5]

Every sepsis and septic shock patient requires to be managed as a medical emergency. Early resuscitation, early antibiotics and early source control once stable have been the crux of sepsis management.

These guidelines were carried forward in the latest 2021 SCC guidelines. However recommendations were made against qSOFA in the backdrop of contradictory results from trials. The elements of initial resuscitation of SSC bundle 2021 are given in Table 2[6]

PICTURE 6 : Initial resuscitation as per SSC 2021
○ Sepsis, septic shock are medical emergencies, and treatment and resuscitation should begin immediately. ○ Measure lactate levels and guide resuscitation to decrease lactate levels ○ Obtain blood cultures prior to administration of antibiotics. ○ Administer broad-spectrum antibiotics within one hour if there is high likelihood of sepsis ○ If in doubt of infection or if there is no shock, broad spectrum antibiotics can be delayed up to 3 hours to assess for alternate diagnosis. ○ Begin rapid administration of 30ml/kg crystalloid for sepsis induced hypoperfusion to be completed in first 3 hours ○ Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg. ○ Admit the patients who or in septic shock to the ICU within 6 hours.

Fluid resuscitation is the mostly done without any cardiac evaluation in the initial stages of shock which is presumed to be due to sepsis. Over resuscitation with fluid in non-responders is detrimental. Positive fluid balance is associated with increased morbidity and mortality in multiple studies which show worse overall mortality in critically ill patients, and increased mortality in patients with acute kidney injury, as well as prolonged recovery in patients with acute lung injury/acute respiratory distress syndrome (FACTT trial)[33]. Increased mortality in septic shock patients (VASST trial)[34] It is also associated with intra-abdominal hypertension.[35]

Increasing fluid overload induces a vicious cycle of interstitial oedema and organ dysfunction. There is now indisputable evidence that volume overload results in multi-organ dysfunction with adverse patient outcomes.[36] The increased venous pressure has profound effects on microcirculatory flow and organ function. The kidney is particularly vulnerable to increased venous pressure, which leads to increased

renal subscapular pressure and reduced renal blood flow. In addition, increased renal interstitial pressure may collapse intrarenal collecting lymphatics compromising lymphatic flow. These effects result in oliguria with a marked decrease in renal function. [37]

But bedside fluid assessment and administration of fluids is mostly guided dynamic indices. Not all the patients who are labelled fluid responders by bedside tests will respond to volume expansion. This false-positive fluid response from these tests could be due to an underlying cardiac dysfunction. [11, 38]

Historically, cardiac function in sepsis has been assessed primarily by left ventricular ejection fraction (LVEF). However, LVEF is highly load dependent and therefore less reliable in assessment of cardiac function in states of low preload or low afterload[26] as in septic shock. Assessing RV function can be considered to identify true non-responders to fluid response.[11]

Several parameters like RV dimensions, Tricuspid annular plane systolic excursion (TAPSE), RV functional area change (FAC), LV and RV end diastolic area (EDA) are used as markers of RV dysfunction.

Antoine Vieillard-Baron et al[39] in their retrospective study included 280 patients with septic shock were analysed. RV failure was defined as RV dilatation and a CVP≥8 mmHg. 41% of patients had no RV abnormality, 17% had RV dilatation without failure and 42% in RV failure. Higher RV size was associated with a lower response to passive leg raising for a given PPV. TAPSE was found to be overlapping in all the subjects and was not specific to RV failure. 63.5% of patients with RV failure had a normal TAPSE.

In a secondary analysis Michael J. Lanspa et al[40] studied echocardiographic parameters on 393 critically ill patients with severe sepsis or septic shock within the first 24 hours of ICU admission. They defined RV dysfunction as FAC < 35% or TAPSE < 1.6 cm. Patients with RV dysfunction (48%) had higher 28-day mortality (31% vs 16%, p = 0.001). They concluded that RV dysfunction was associated with increased mortality while LV systolic dysfunction was not.

In another retrospective cohort study[41] using a prospective registry of septic shock from January 2011 and April 2017, of 778 septic shock patients who underwent echocardiography, 270 (34.7%) showed SCM. Among them, 67.3% had LV systolic dysfunction, 40.7% had RV dysfunction and 39.3% had LV diastolic dysfunction. LV dysfunction was common but Multivariate analysis showed that isolated RV dysfunction was an independent risk factor of 28-day mortality (OR 2.26, 95% CI 1.04 to 4.91).

Winkelhorst JC et al[42] conducted a Single-centre retrospective cohort study in adult patients admitted to the ICU with severe sepsis and septic shock. RVEF was recorded as an average over the first 24 h. Patients were separated into subgroups according to their RVEF: RVEF less than 20% (A), RVEF 20% to 30% (B), and RVEF more than 30% (C). The primary endpoint was 1-year all-cause mortality. RVEF was independently associated with 1-year all-cause mortality.

A Meta-analysis of 1,373 Patients Vallabhajosyula S et al[43] reviewed the published literature from January 1999 to April 2020 for studies evaluating adult patients with sepsis and septic shock. Study definition of RV dysfunction was used to classify patients. The primary outcome was all-cause mortality divided into short-term mortality (ICU stay, hospital stay, or mortality ≤30 days) and long-term mortality (>30 days). In this meta-analysis of observational studies, RV dysfunction was associated with higher short-term and long-term mortality.

In an Indian study[44] aimed to analyse the echocardiographic indices of the right heart in septic shock adult patients. 88 septic shock patients were enrolled and right heart analysis was done with TTE. They concluded that right heart abnormalities of chamber dimension and systolic and diastolic function existed in 79, 25, and 86 % of patients, respectively. They reported that RV subcostal wall thickness, pulse Doppler myocardial performance index, and E/E′ were the predominant abnormalities. However, these abnormalities did not signify poor survival in their studies.

MATERIAL AND METHODS

Source of data: Patients admitted with septic shock in the Intensive Care Units of Dayanand Medical College and Hospital, Ludhiana, and fulfilling inclusion and exclusion criteria were included in the study.

Study design: Prospective observational study

Study place: Intensive care units, Dayanand Medical College and Hospital, Ludhiana

Duration of the Study: June 2021 to December 2022

METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA:

- Patients admitted to ICU with shock and requiring norepinephrine to maintain a MAP > 65 mmhg.
- Lactates > 2 Mmol/l
- Cause of shock presumed to be due to sepsis, as defined by 2016 Sepsis-3 guidelines.[16]
- Aged 16-70 years

EXCLUSION CRITERIA:

- Known history of any prior cardiac disease or any type of atrial-ventricular block on baseline ECG.
- Known history of COPD / ILD / morbid obesity/ OHS.
- Regional wall motion abnormality of LV on Echocardiography
- Inability to acquire any of the required echocardiographic parameter.
- Refusal to participate.

OUTCOME:

Identifying RV dysfunction in sepsis

RV dysfunction as poor prognostic indicator with respect to AKI and Mortality.

DATA COLLECTION AND METHODS:

Patients admitted to the ICUs septic shock meeting the SEPSIS -3 (2016) criteria for septic shock and fulfilling the inclusion and exclusion

criteria for this study were enrolled. Prior written informed consent was taken from the patient or legal representative as appropriate.

Patients were resuscitated and treated as per SSC guidelines. Patients with septic shock were initially resuscitated with crystalloids at 30ml/kg started within 1 hour and completed in 3 hours. Simultaneously with initial resuscitation, if the MAP remained less than 65 mm Hg then nor-epinephrine was started as the first line vasopressor Nor-epinephrine infusion was started at a dose of 0.05µg/kg/min and gradually increased to target MAP >65mmhg. Baseline ABG and lactates were recorded.

TRANSTHORACIC ECHOCARDIOGRAPHY (TTE)

On admission to ICU baseline TTE functional assessment was done by trained echocardiographers (at least 1 year experience). For this study we used a Sonosite ultrasound system with a 1-5MHz probe.(Sonosite Edge II; Sonosite, Inc., FUJIFILM).

Echocardiographic Assessment was done as per American Society of Echocardiography guidelines. [45]

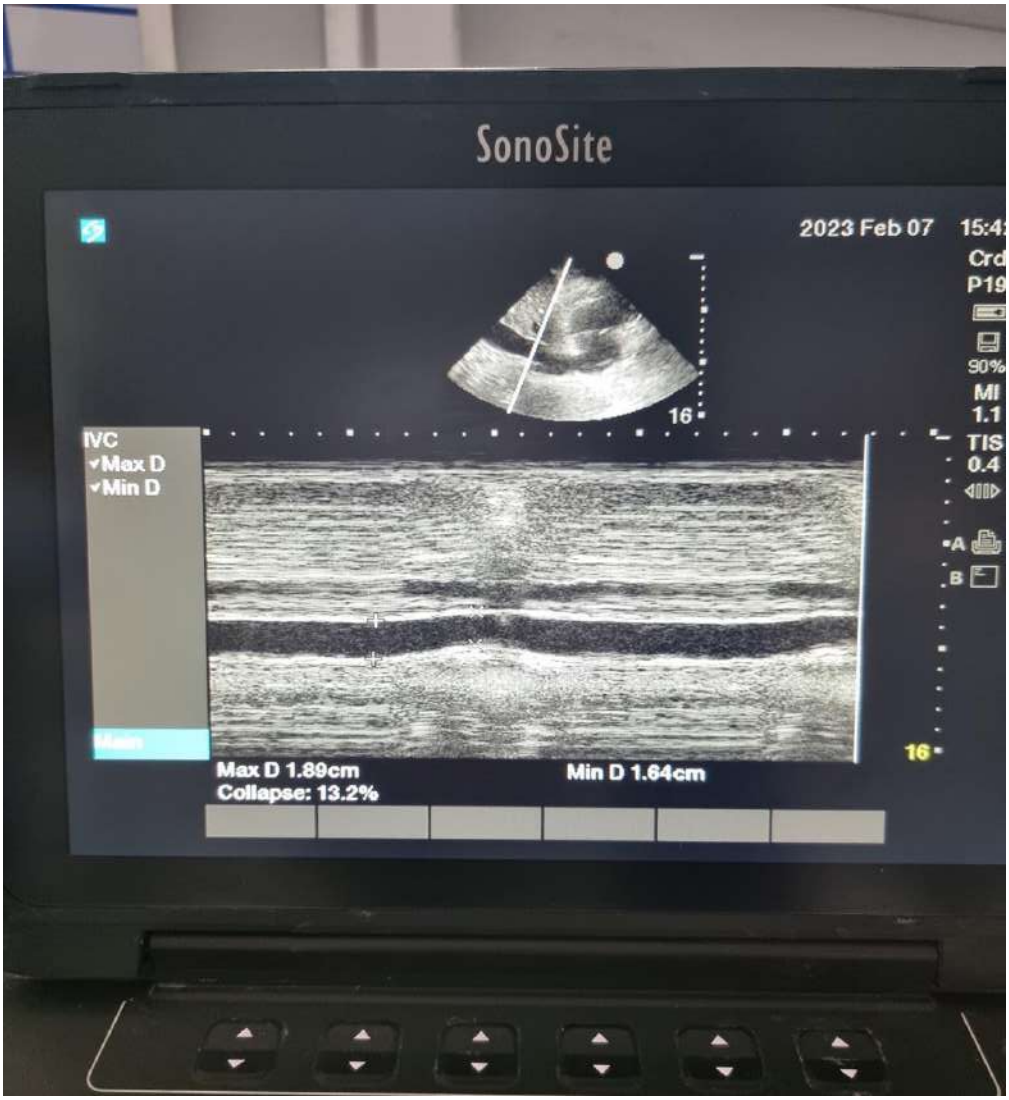
TTE will comprise of

- Left ventricular ejection fraction- LVEF (%),
- LV wall motion assessment,
- Left Ventricular End Systolic Area - LVESA (cm^2),
- Left Ventricular End Diastolic Area - LVEDA (cm^2),
- Right Ventricular End Systolic Area - RVESA (cm^2),
- Right Ventricular End Diastolic Area - RVEDA (cm^2),
- Left Ventricular End Systolic Volume - LVESV (ml),
- Left Ventricular End Diastolic Volume - LVEDV (ml),
- Tricuspid annular plane systolic excursion - TAPSE (mm),
- Tricuspid Regurgitation velocity- TRmax (m/s),
- Pulmonary Arterial Systolic Pressure – PASP (mmhg)
- FAC = (RVEDA-RVESA) *100/RVEDA.
- PASP = $4(TRmax)^2$ + RA pressure
- RV/LV ratio will be calculated RVESA/LVESA, and > 0.6 indicates RV dilatation

- **PICTURE 7 : RA Pressures were calculate based on inferior vena cava (IVC) measurements.**[46]

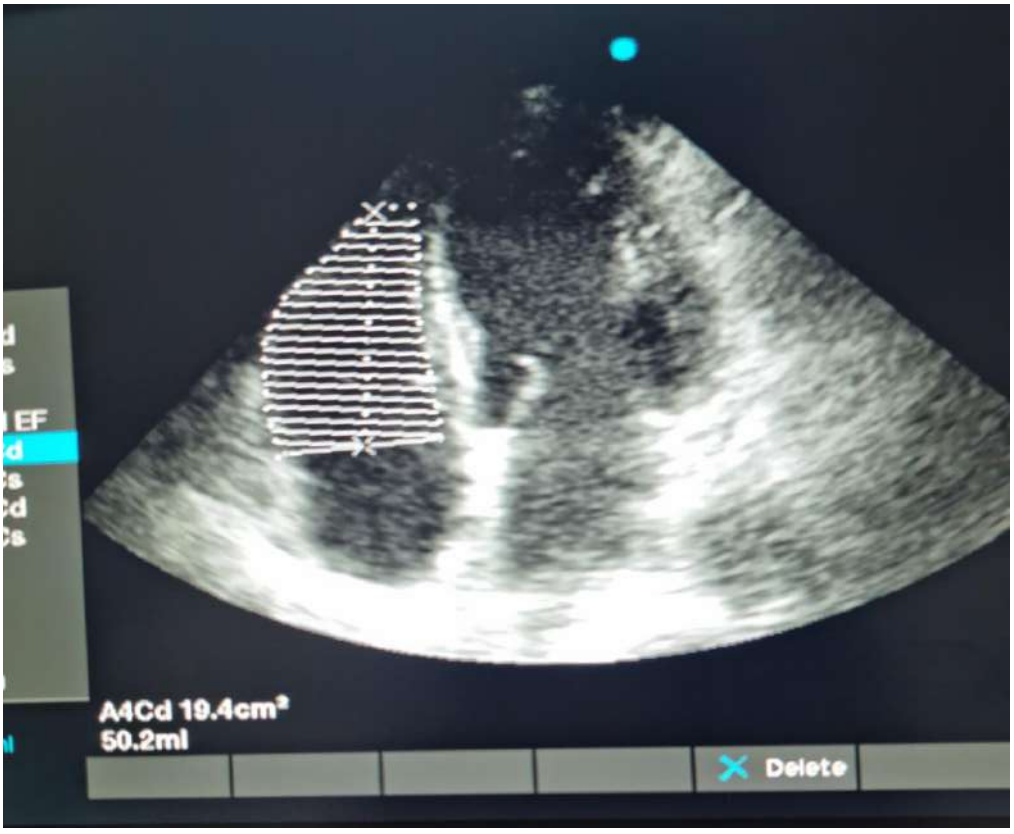
IVC measurement	RA pressure
≤ 2.1 cm collapsing >50% with a sniff	3 mm Hg
>2.1 cm collapsing < 50% with sniff	15 mm hg
Any value in between	8 mmhg

PICTURE 8: IVC size and compressibility measurement.

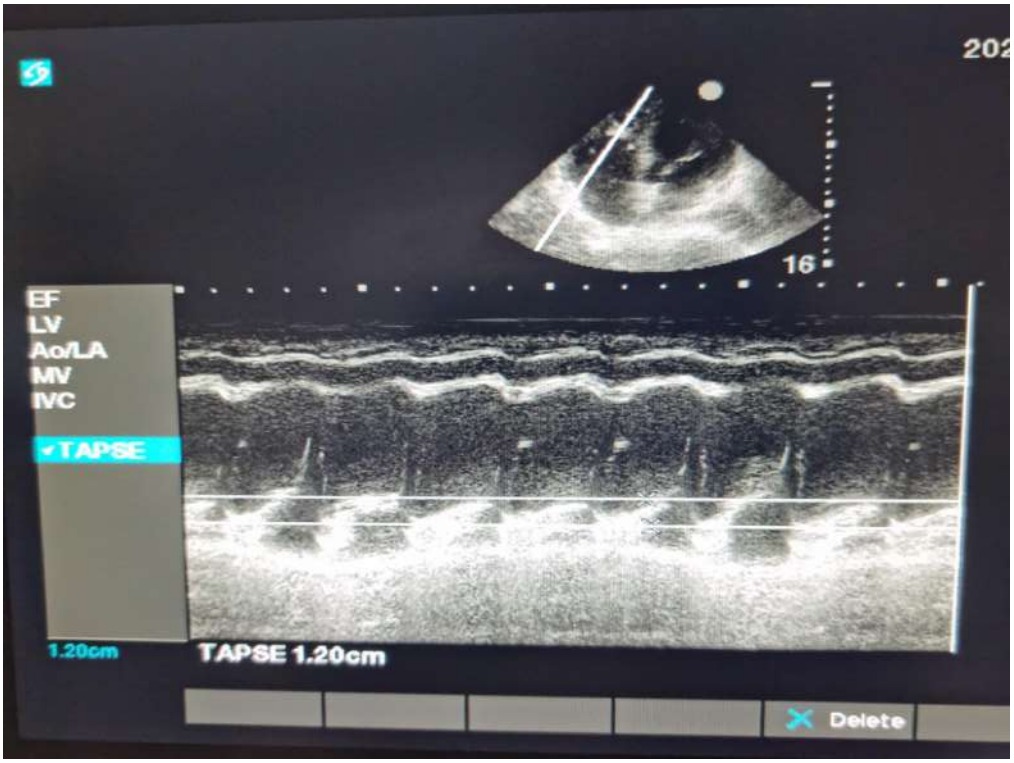


PICTURE 9: Apical 4 chamber view to analyse both LV and RV

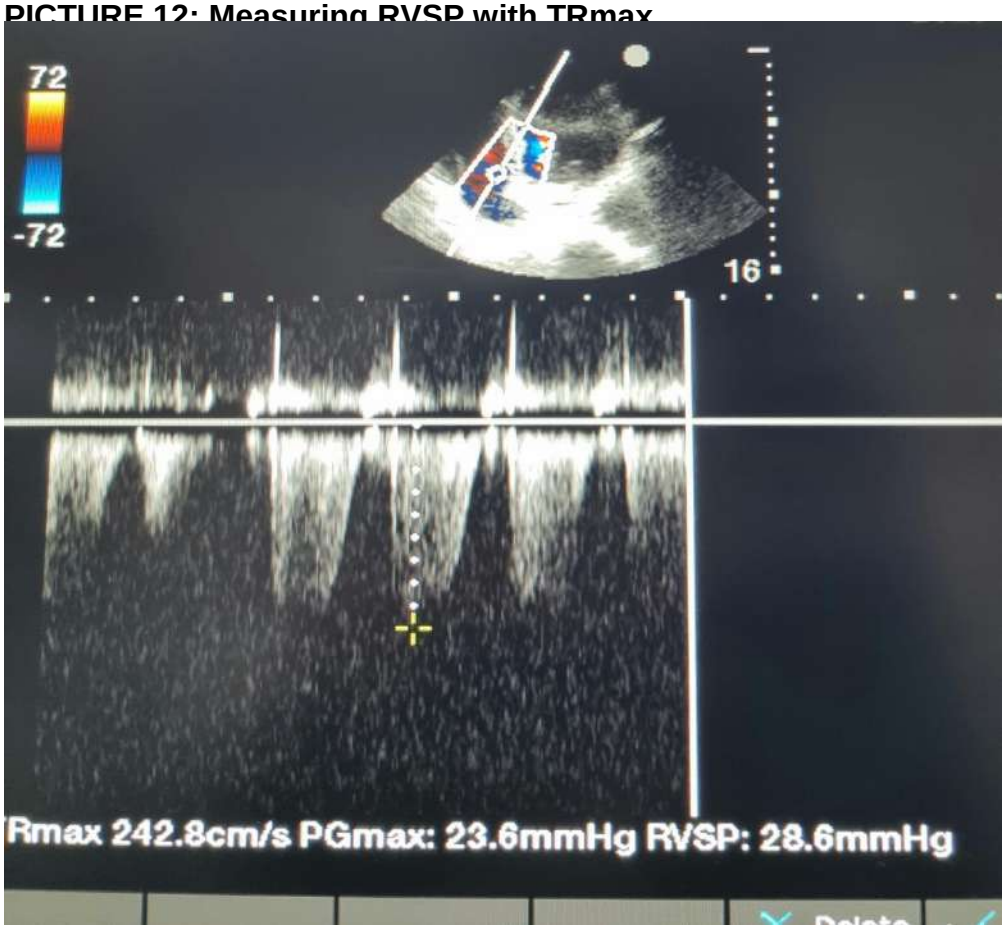
PICTURE 10: Measuring RVEDA to calculate FAC and RVEDA/LVEDA.



PICTURE 11: Measuring TAPSE.



PICTURE 12: Measuring RVSP with TRmax



DEFINING RV DYSFUNCTION IN THE STUDY

Based on the American Society of Echocardiography guidelines[46] and previous studies[39,40] RV function was assessed by TAPSE, RV FAC, LV and RV end diastolic area (EDA) and RA pressures calculated by IVC. As all these parameters have varying sensitivity and specificities in identifying RV dysfunction, in the present study RV dysfunction was defined as presence of any of the below. [39,40]

- TAPSE < 16 mm,
- RV functional area change (FAC) <35%.
- RVESA/LVESA > 0.6 with a RA pressure > 8 mmhg

LV dysfunction was defined as EF < 45%.

Parameters collected:

Following data were recorded: HR, systolic, diastolic and mean arterial pressures, vasopressors doses, lactate, and urine output.

Age, past medical history of any comorbidities, hemogram, RFT, serum electrolytes, LFT, Chest X-ray and SOFA score.

Follow up-

Duration of vasopressors, occurrence of AKI as per KDIGO guidelines[47], Number of days in ICU , mechanical ventilation requirement if any and duration of ventilator and 28 day mortality.

Endpoints:

Identification of RV dysfunction in septic shock.

RV dysfunction as a corelating factor for AKI and Mortality.

STATISTICAL ANALYSIS

Sample size:

Prevalence of septic shock admitted in ICU as taken from an Indian study was as 6.2 %.[48]

Based on this, sample size (n) was calculated using formula

$n = z^2 * p * (1 - p) / e^2$

$z = 1.96$, $p = 0.062$, $e = 0.05$

$n \approx 90$ patients needed.

100 patients will be included in the study to increase the power of the study.

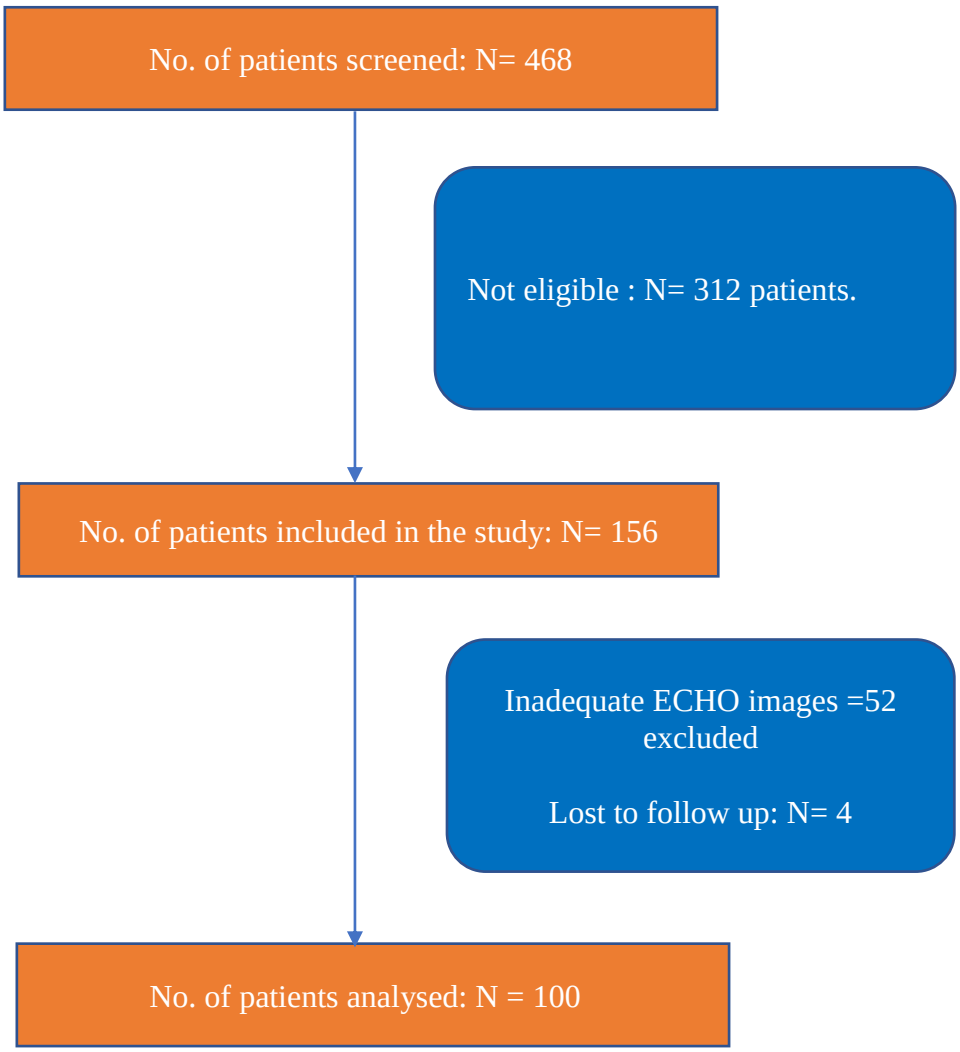
Data were described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using Mann Whitney *U* test for independent samples for non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and fisher exact test was used when the expected frequency is less than 5. Covariates obtaining a P value <0.05 in the univariate analyses were included in the multivariate Binary logistic regression analyses. Receiver operator characteristics (ROC) curve was done, and criterion value was estimated depending on the specificity and sensitivity. Area under curve (AUC) was measured. A probability value (*p* value) less than 0.05 was considered

statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

A total number of 468 septic shock patients admitted to intensive care units of the hospital were screened for eligibility. Out of 468 septic shock patients screened, 312 patients were not recruitable based on inclusion and exclusion criteria. In 52 patients adequate echocardiographic images were not obtained and were excluded from the study. 4 patients could not be followed for 28 days. 100 patients were analysed during the 18 months study period.

Figure 1: Trial profile


No. of patients screened: N= 468
Not eligible : N= 312 patients.
No. of patients included in the study: N= 156
Inadequate ECHO images =52 excluded
Lost to follow up: N= 4
No. of patients analysed: N = 100

Data depicted as N= number

Demographic data and patient characteristics:

The mean age of the patients included in the study was 50.49 ± 15.59 years. Majority of patients were in the age group between 37 and 62 years.

Figure 2: Age distribution

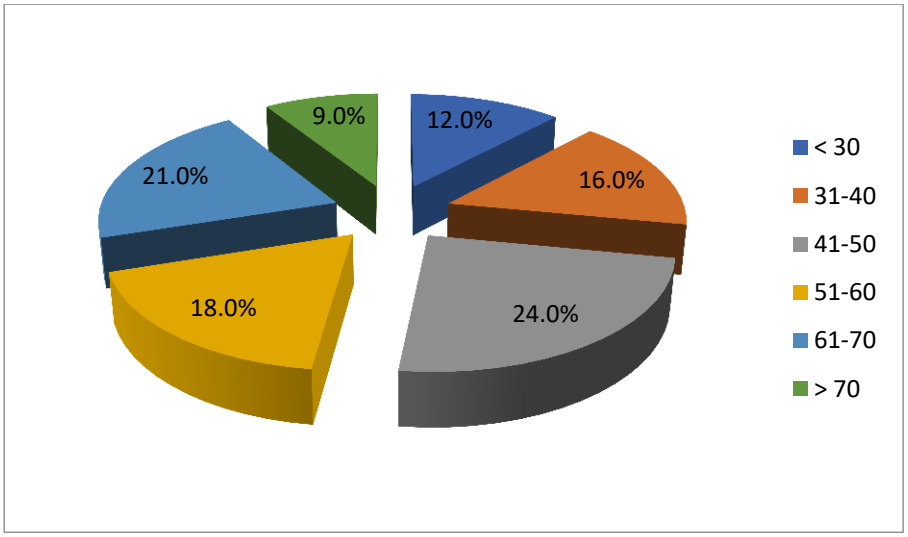
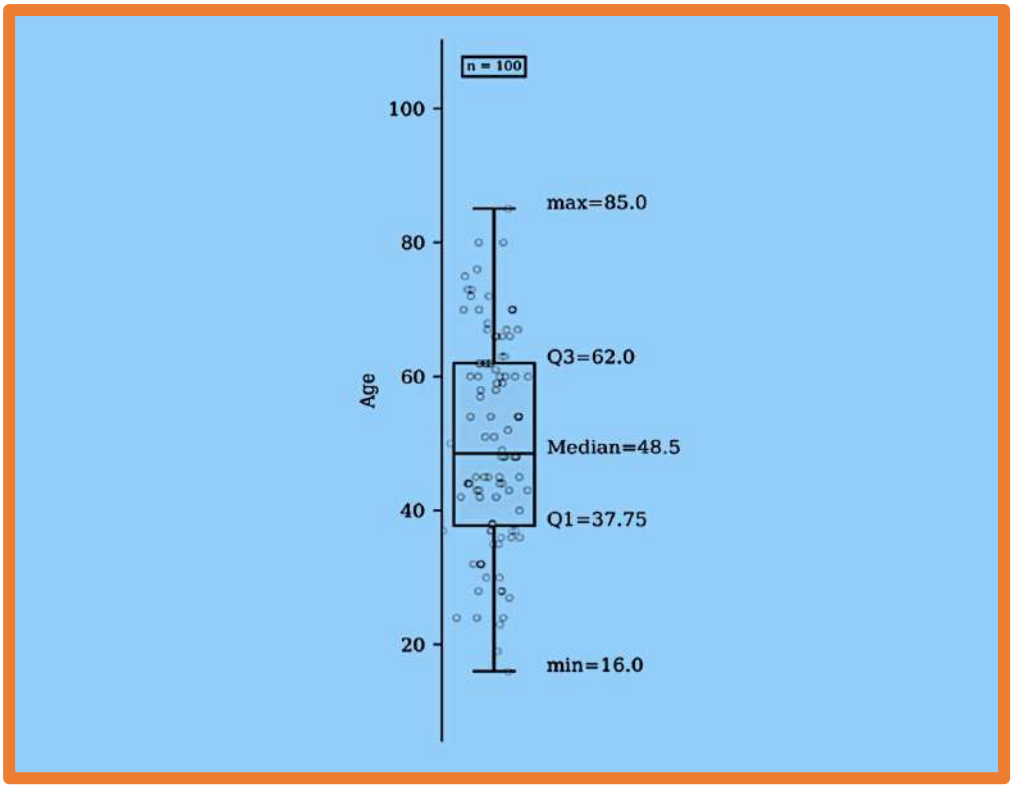
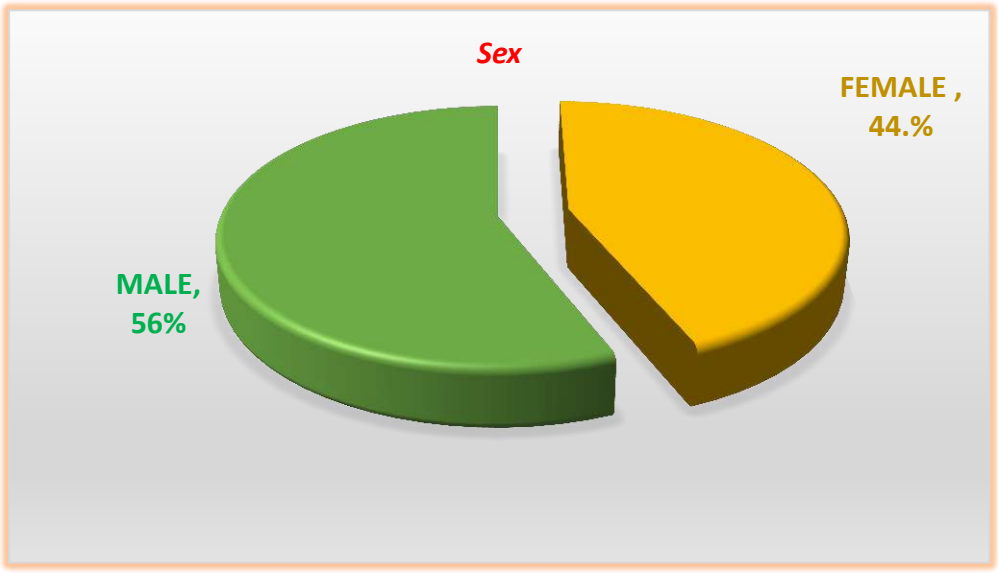


Figure 3: Box graph showing age distribution



There were 56 males and 44 females in the study population.

Figure 4: Gender distribution



Mean weight of the patient population was 79.31±10.1 kgs and mean BMI was 28.29±3.85 Kg/mt^2

Figure 5: BMI distribution

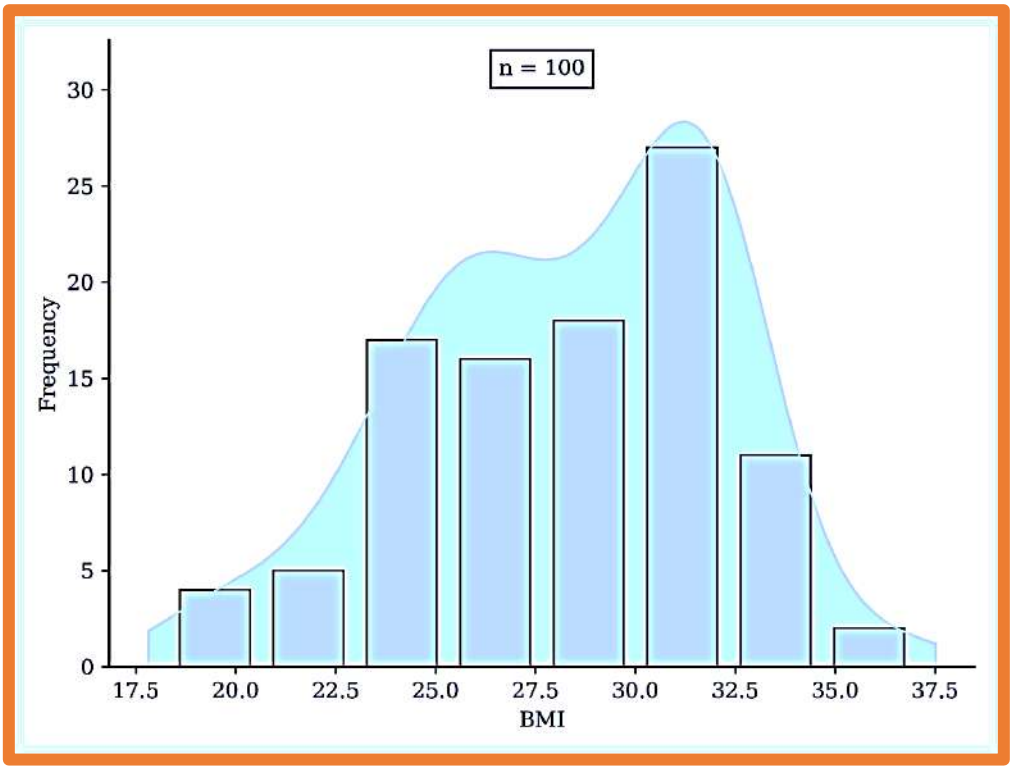
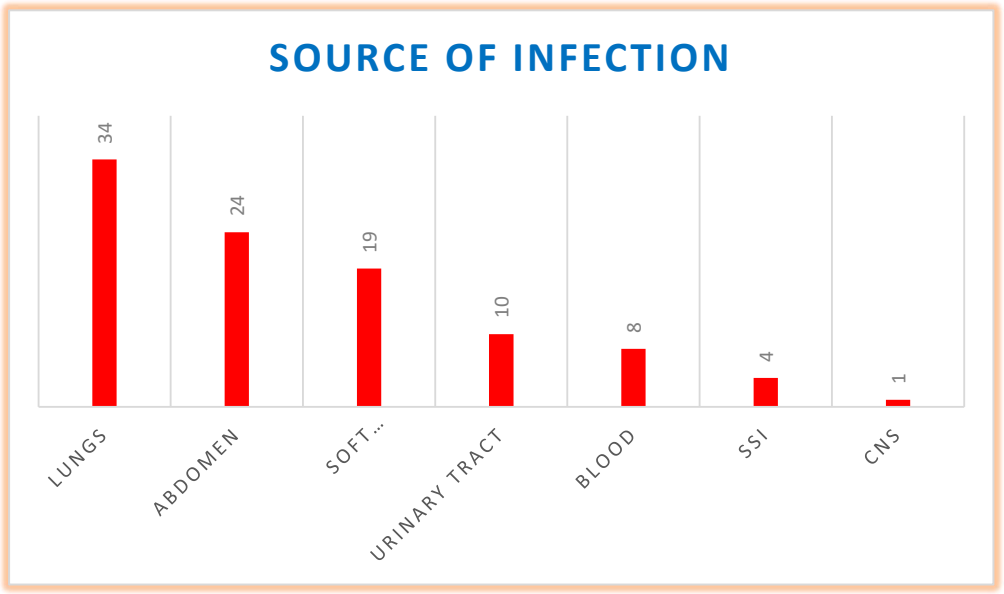


Figure 6: Source of infection



SSI- Surgical Site Infection, CNS – Central Nervous System

Most common source of infection were lungs followed by abdomen and soft tissue infection.

Table 1: Demographic profile and characteristics of the study:

Parameters	Number of patients (%)
Age (years)	50.49±15.59
Sex:	
Males	56 (56%)
Females	44 (44%)
Weight (Kg)	79.31±10.1
BMI (Kg/mt^2)	28.29±3.85
Primary source of infection:	
Lung	34 (34%)
Abdomen	24 (24%
Soft tissue/ Head neck	19 (19%)
Urinary tract	10 (10%)
Blood	8 (8%)
SSI	4 (4%)
Central nervous system	1 (1%)

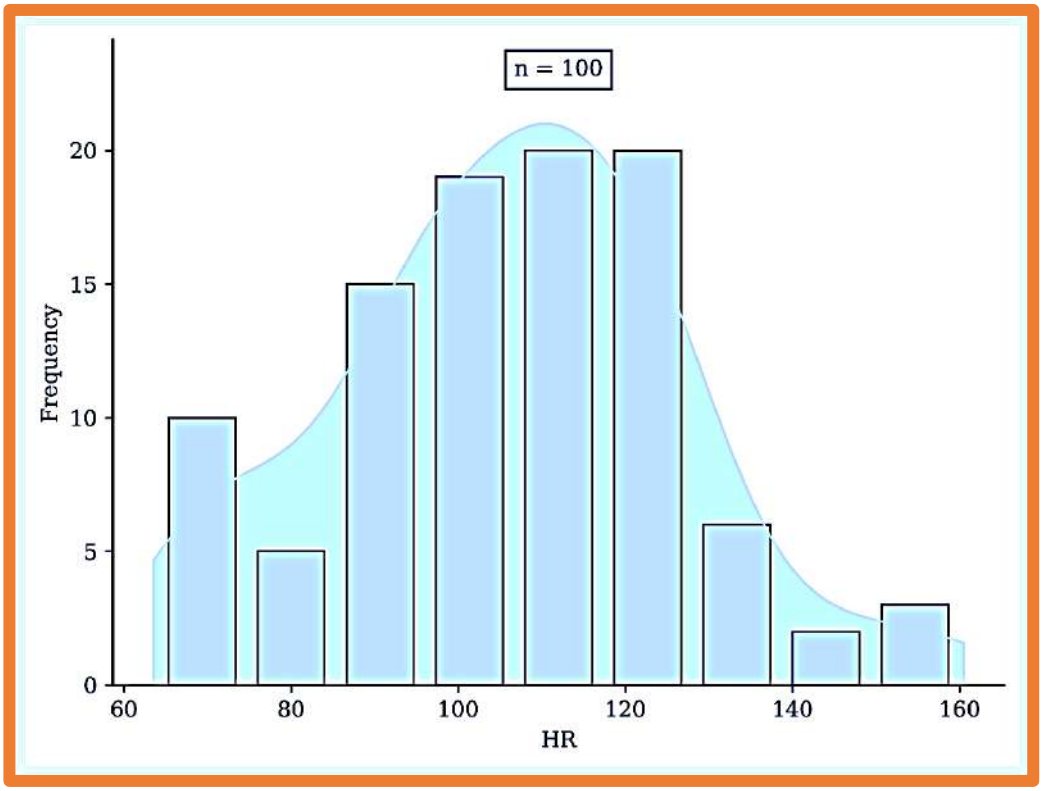
% = percentage, Kg = Kilogram, mt = meter

Table 2: Parameters during the assessment

	Minimum	Maximum	Mean	Std. Deviation
HR	64	160	106	21
MAP (mmhg)	46	98	68.28	9.21
SOFA	2	21	8.69	3.77
Lactates (mmol/L)	2	15	4.15	2.37

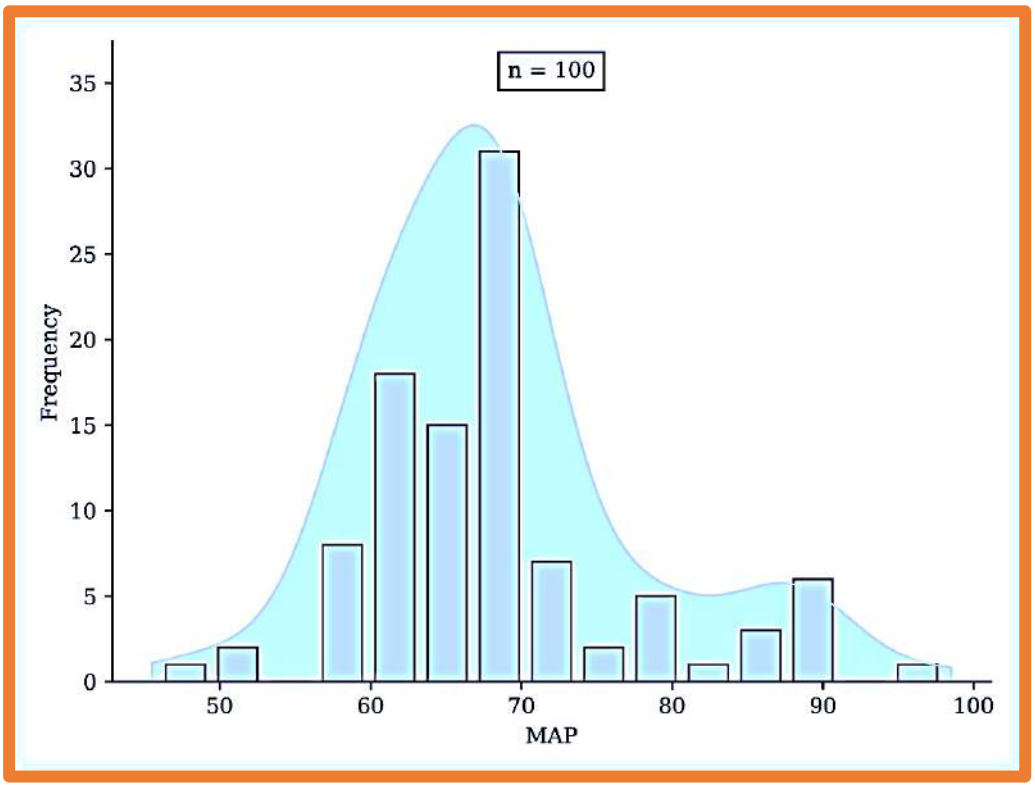
Mean HR was 106±21 beats per minute.

Figure 7: Heart Rate among the patients



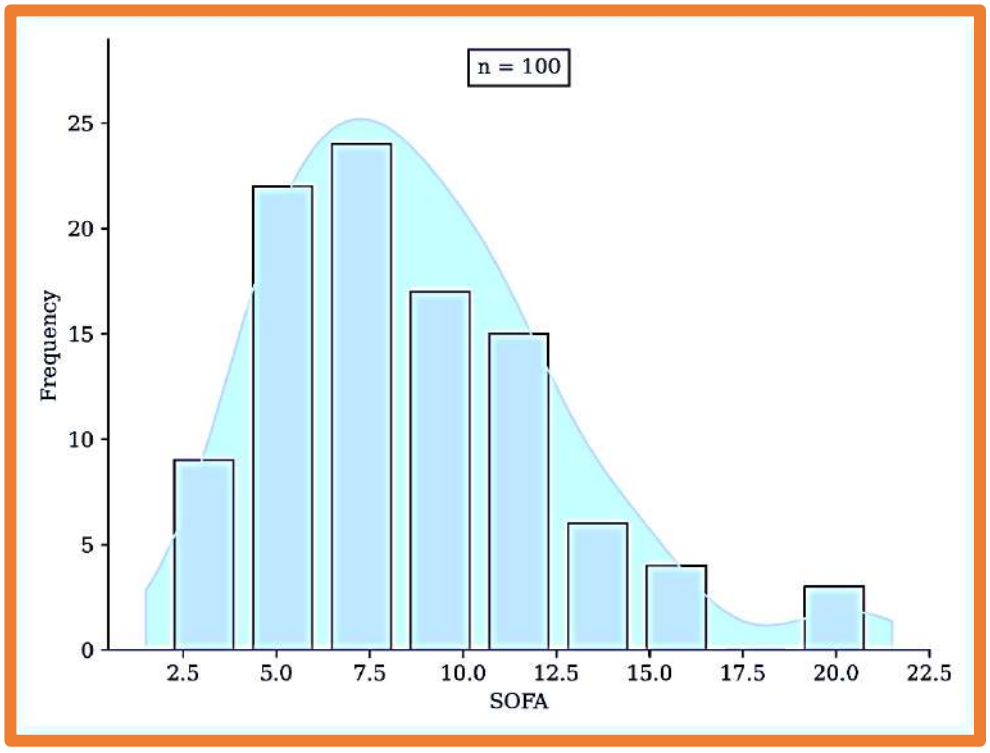
Mean value of MAP was 68.28±9.21 mmhg

Figure 8: MAP among the patients



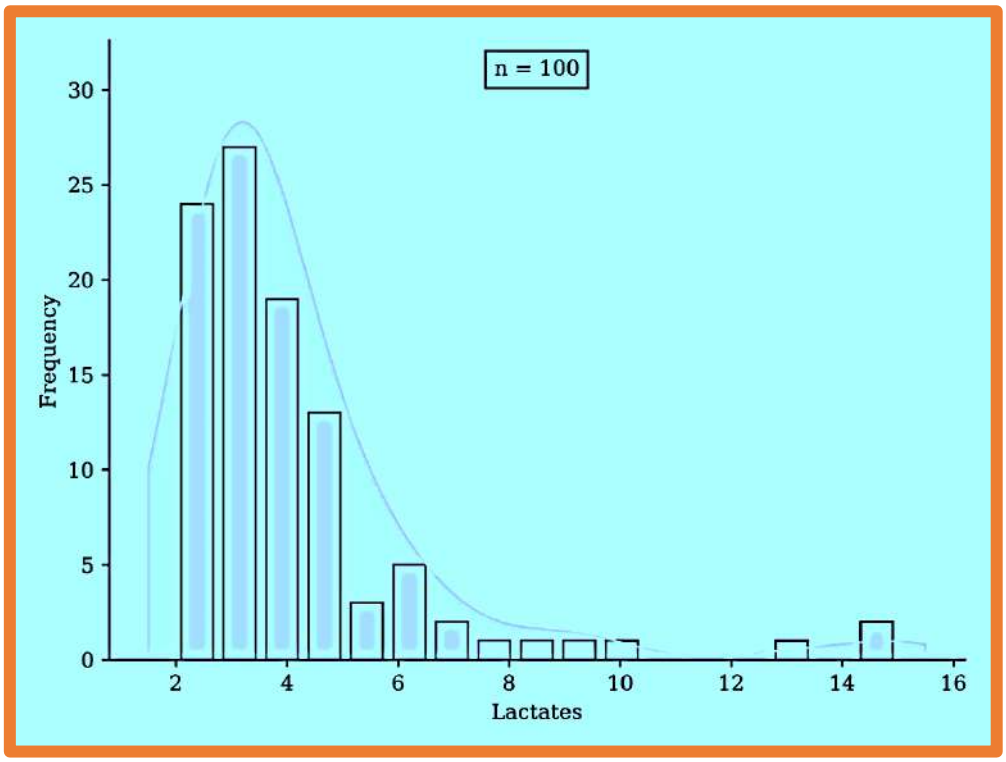
SOFA values had a a mean value of 8.69 ±3.77.

Figure 9: SOFA score among the subjects



Baseline lactates were measured. Lactates had a mean value of 4.15 ±3.27.

Figure 10: lactates distribution



63 people were put on mechanical ventilation during the 28 days course

Figure 11: Mechanically ventilated patients

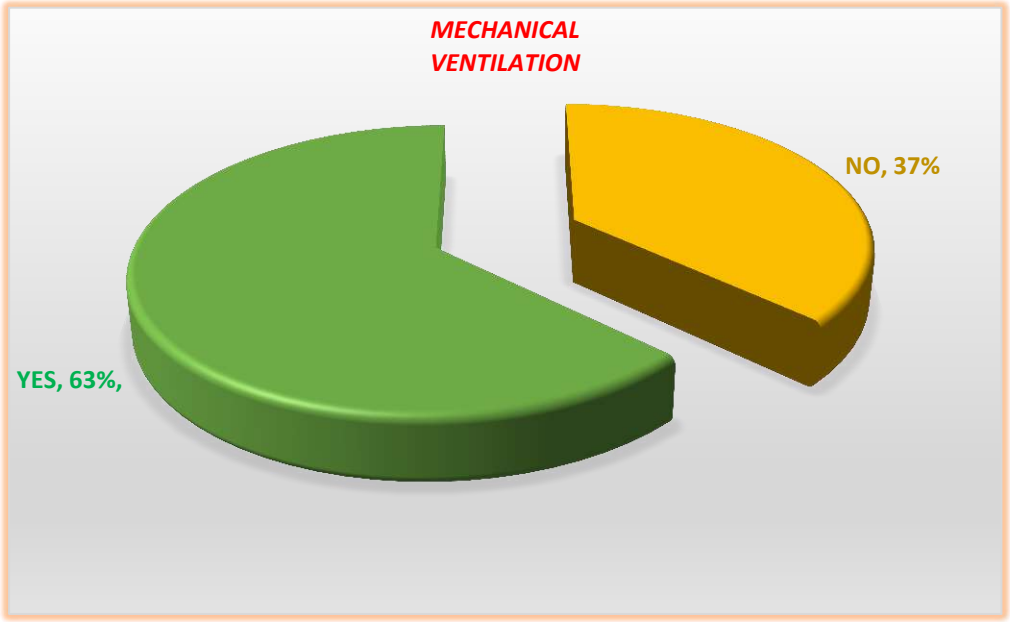
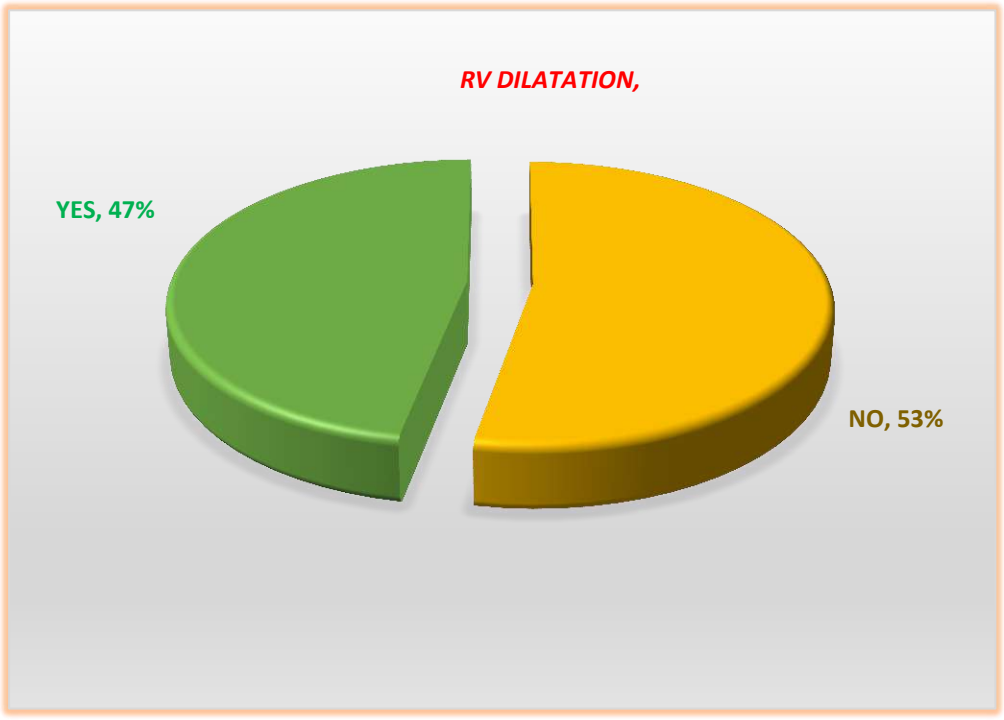


Table 3: Echocardiographic Findings

	Mean	Std. Deviation	Minimum	Maximum
RA (cm)	4.07	0.68	2.38	5.80
RV basal (cm)	3.94	0.56	2.71	5.20
RV mid Cavity (cm)	3.40	0.58	2.18	4.88
RV Longitudinal (cm)	7.82	0.93	5.78	9.96
TR max (m/s)	175.82	76.19	46.70	325.00
PASP (mmhg)	31.72	14.61	11.00	67.00
TAPSE (mm)	19.09	5.01	6.10	31.00
RVESA (cm.sq)	13.80	3.31	9.20	22.60
RVEDA (cm.sq)	22.22	4.61	14.60	36.40
FAC (%)	37.49	9.90	11.76	56.77
LVEDA (cm.sq)	37.17	6.54	20.80	53.80
RV/LV	0.60	0.09	0.42	0.89
RAP (mmhg)	10.61	4.99	3.00	15.00
LVEDV (ml)	116.81	32.96	46.50	231.90
LVESV (ml)	60.19	17.37	19.40	107.00
EF (%)	46.99	14.07	15.18	68.41

Figure 12: RV Dilatation in all patients



47% had RV dilatation and in total 35% had both RV dilatation and RA pressures more than 8mmhg.

Figure 13: RV Dilatation + RAP >8 mmhg

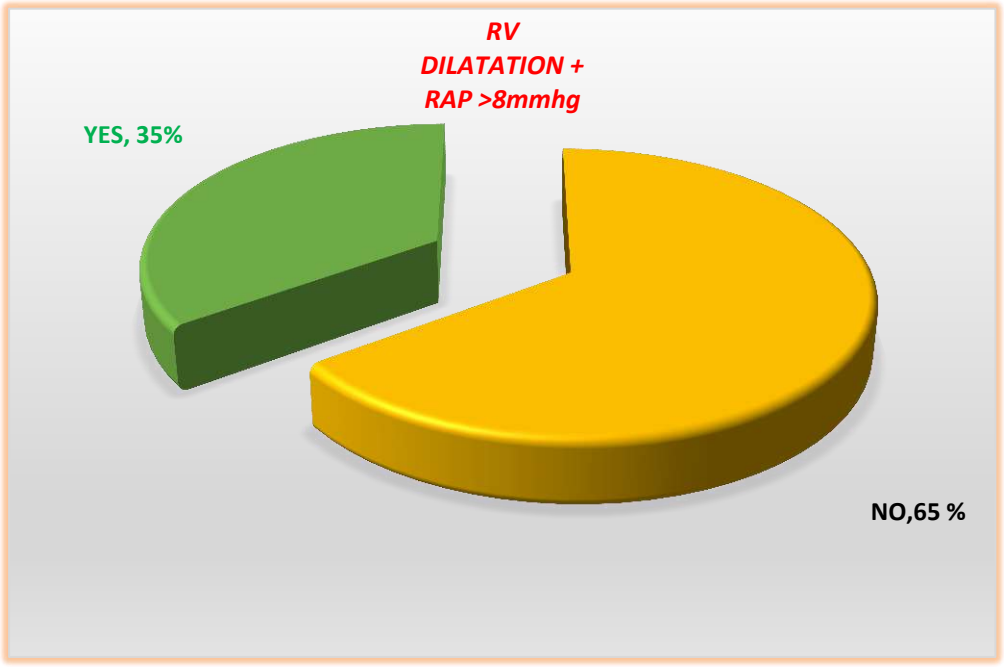


Figure 14: TAPSE Distribution

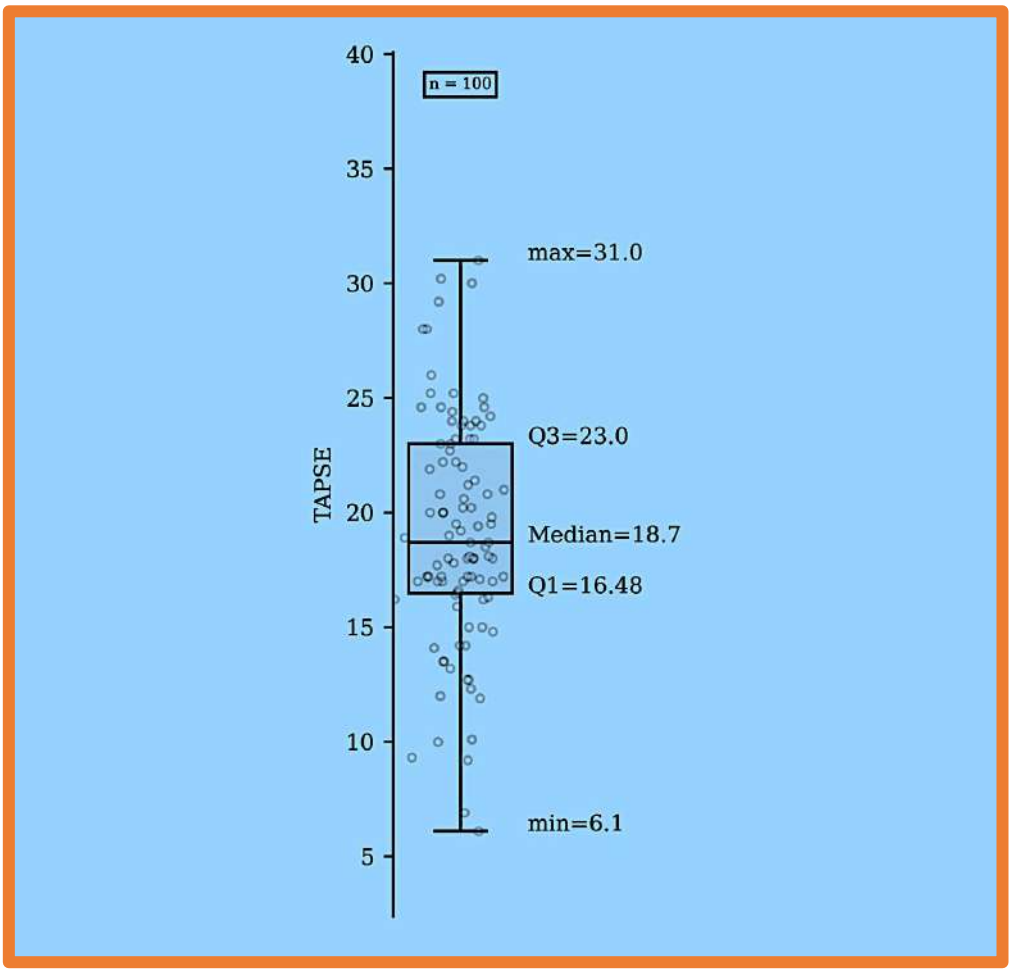
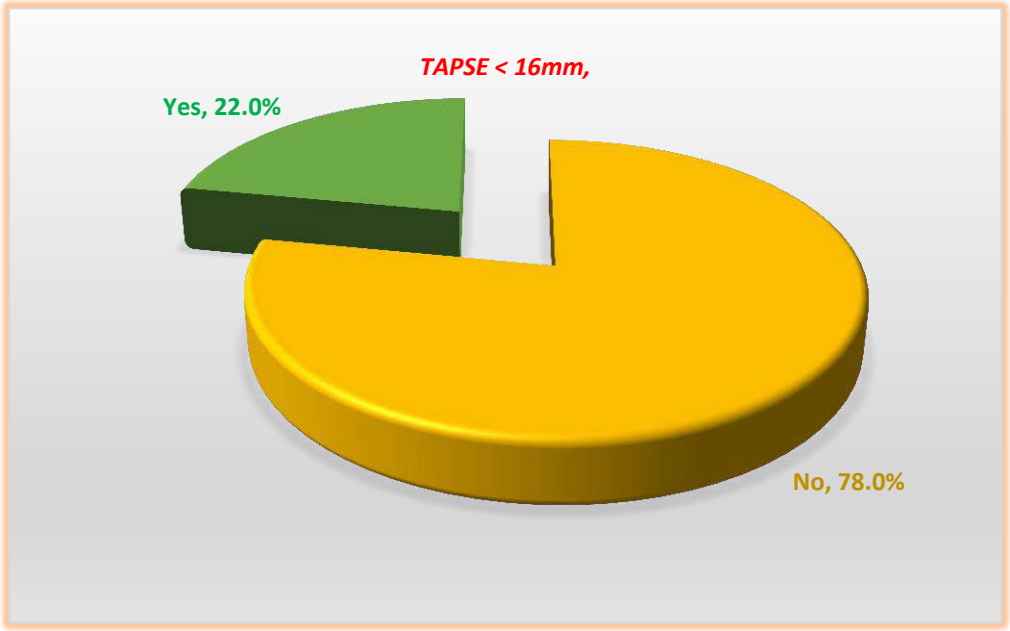


Figure 15: TAPSE < 16mm



TAPSE being used as one of the defining parameter for RV function was <16 mm only in 22%.

Figure 16: FAC distribution

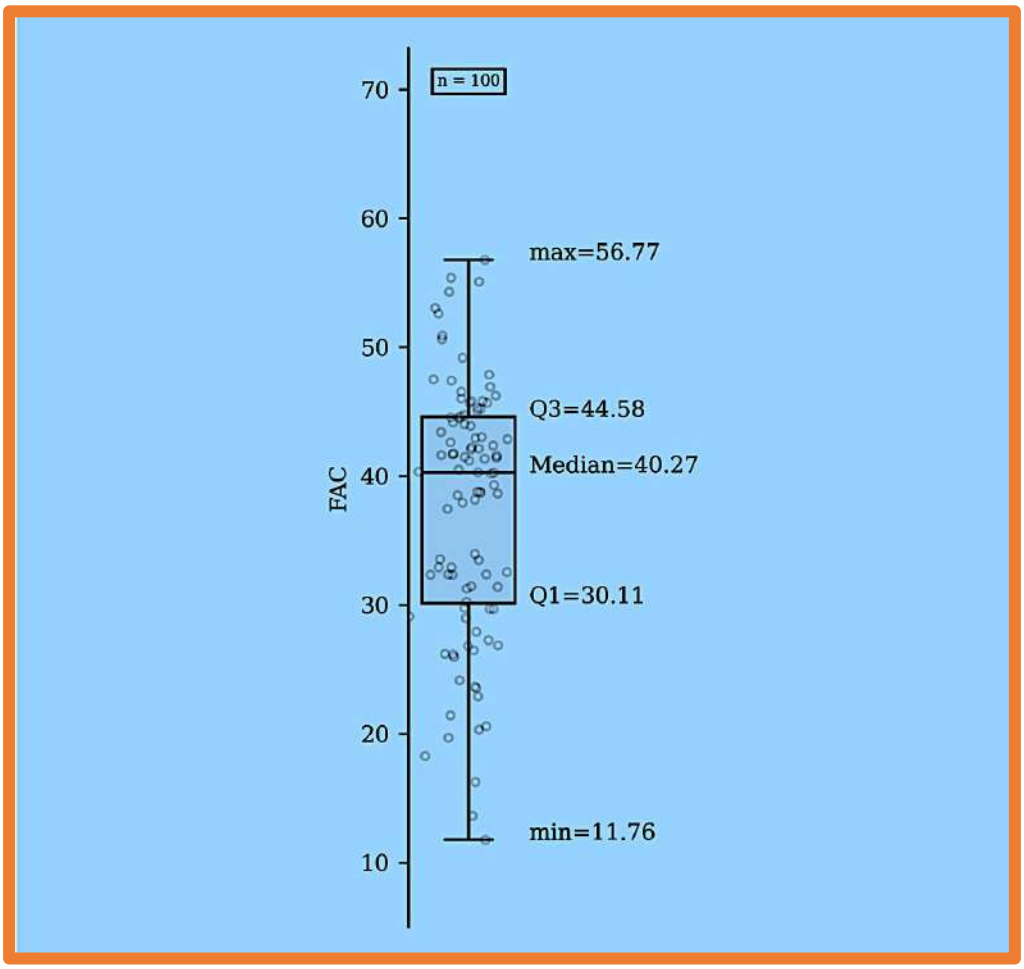


Figure 17: FAC <35 %

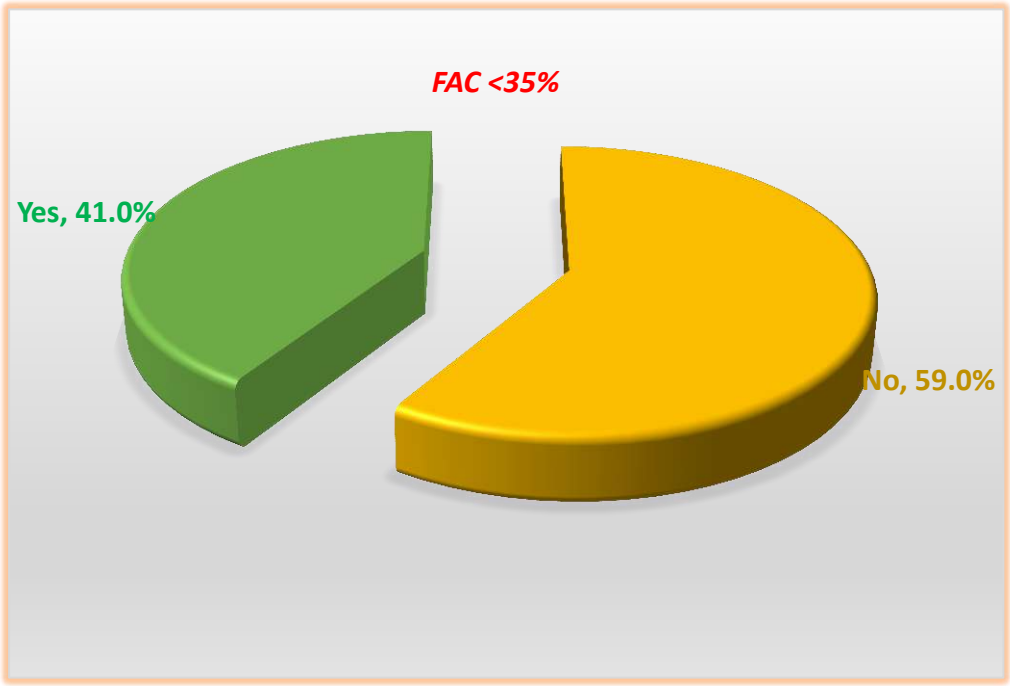
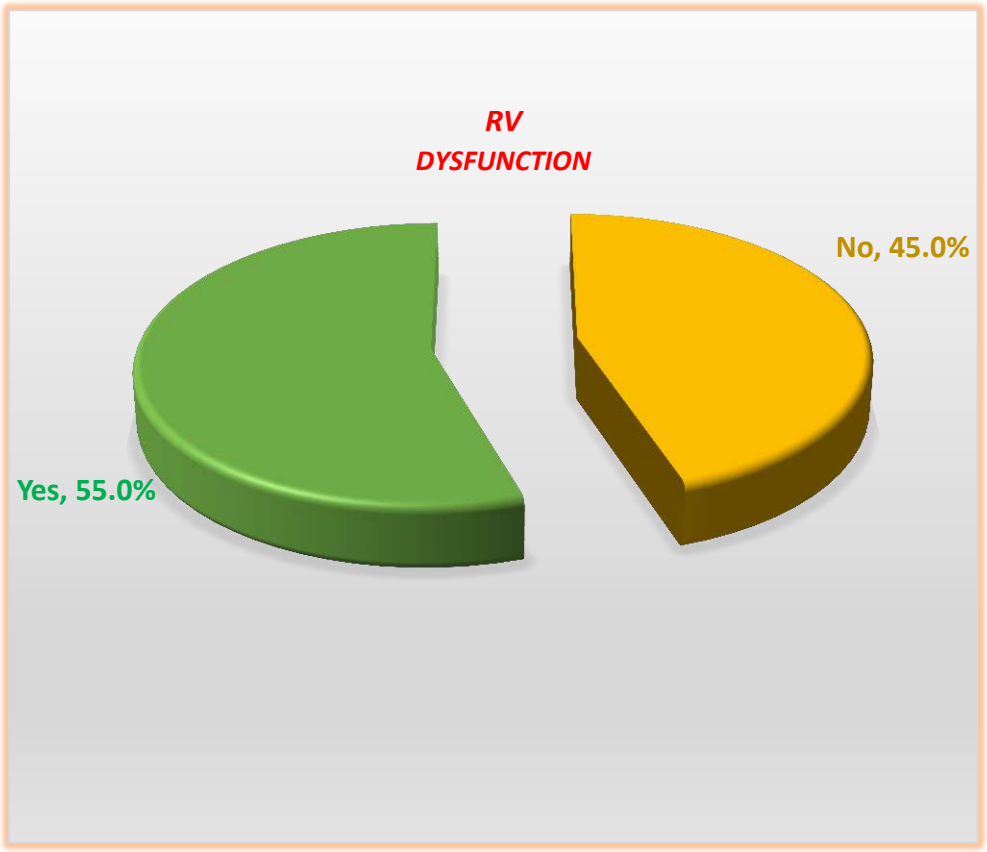


Figure 18: RV dysfunction incidence



The three criteria were used for defining RV dysfunction.

- TAPSE<16mm was only in 22 %
- FAC <35 % was present in 42 %
- RV dilatation with raised RA Pressures was present in 35%

Presence of any of the above was taken as RV dysfunction and the incidence of RV dysfunction was 55%.

Figure 19: EF distribution

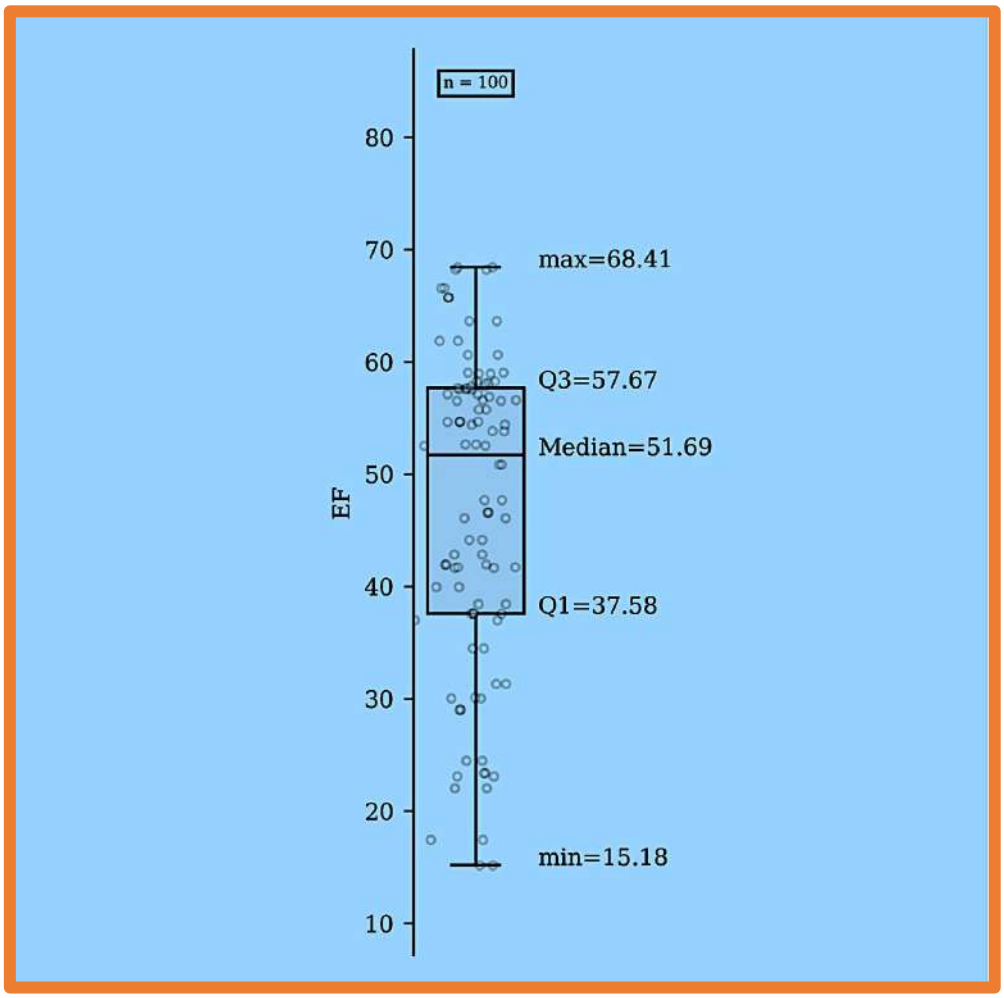
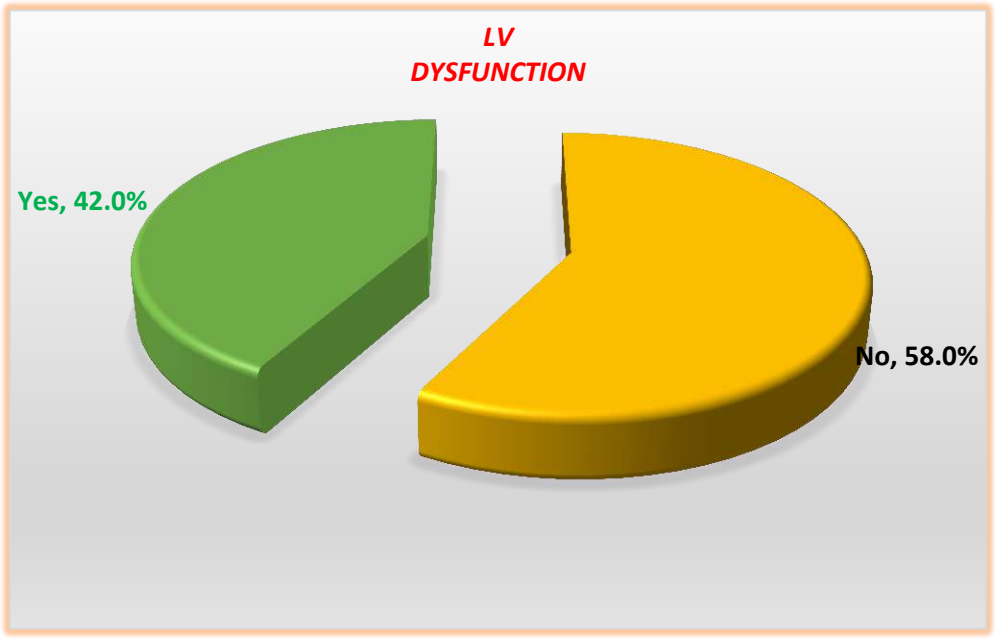
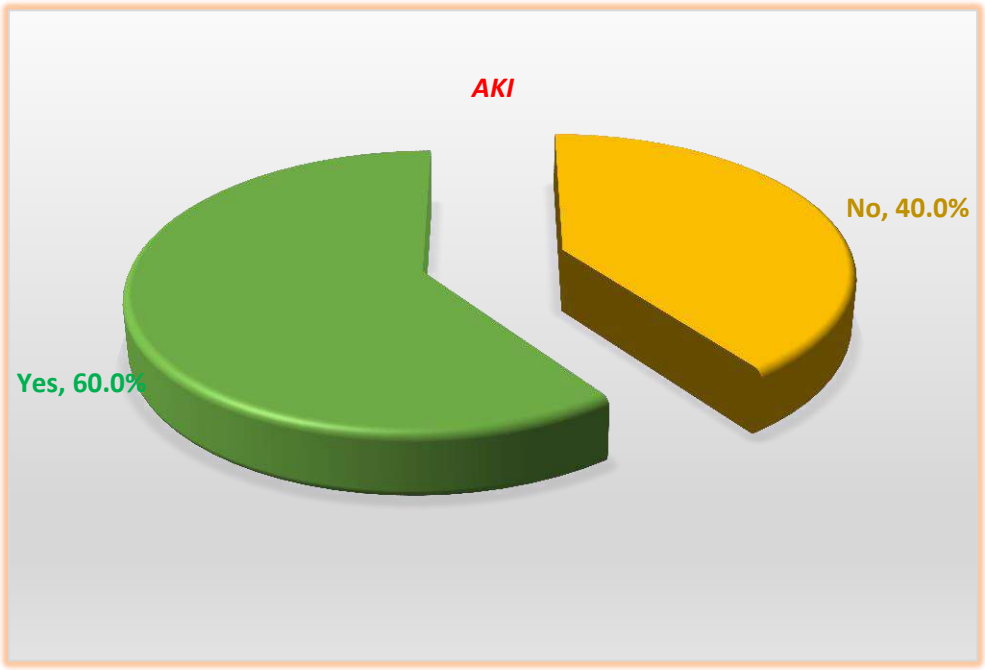


Figure 20: LV dysfunction



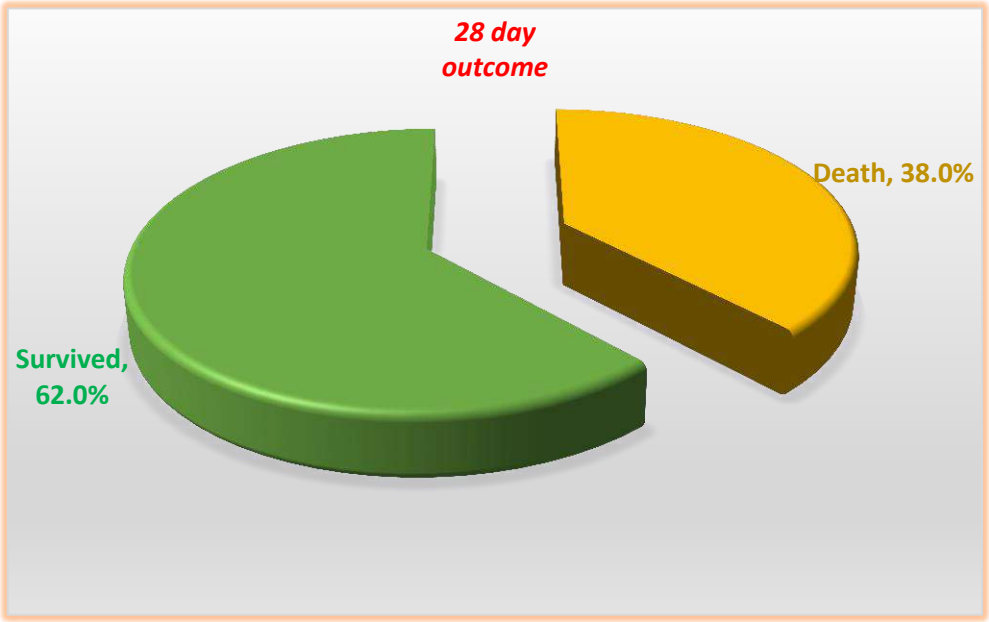
42% had LV dysfunction among the study population

Figure 21: AKI



Overall incidence of AKI was 60% in the study population

Figure 22: 28-day Outcome



All-cause mortality by the end of 28 days was 38% in septic shock.

Table 4: Durations of vasopressors, mechanical ventilation and ICU in all patients.

	Mean	Std. Deviation	Minimum	Maximum
Duration of Vasopressors	3.89	2.11	1.00	9.00
Duration of mechanical ventilation	6.17	7.04	0.00	30.00
Duration of ICU stay	9.74	6.44	1.00	30.00

Figure 23: Duration of vasopressors, mechanical ventilation and ICU in all patients.

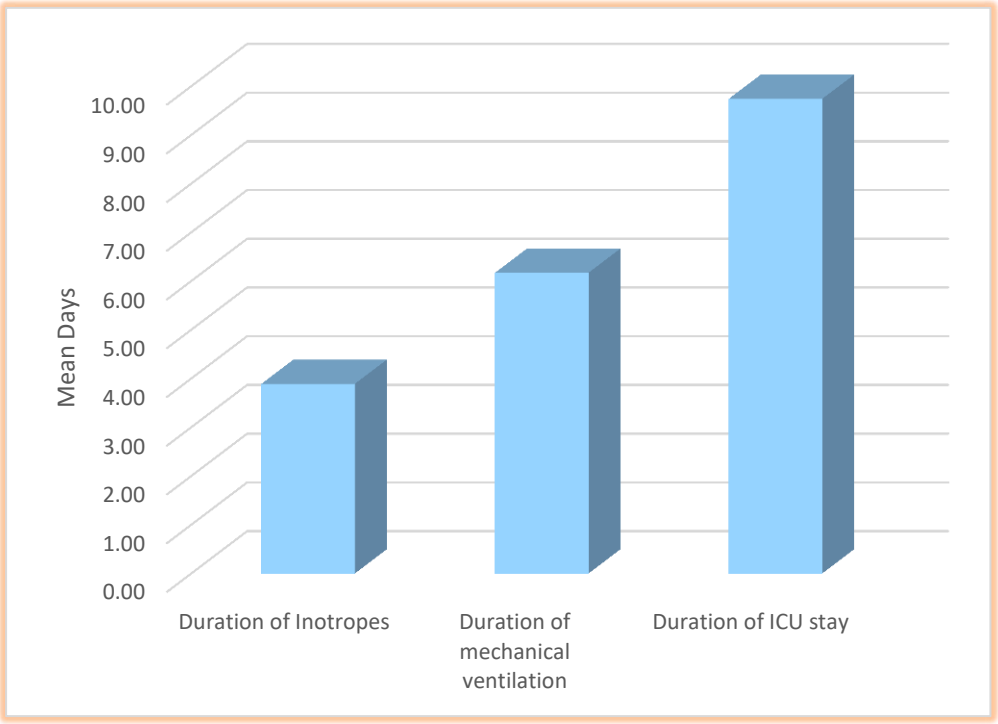


Figure 24: Duration of vasopressors, mechanical ventilation and ICU in survivors and non survivors.

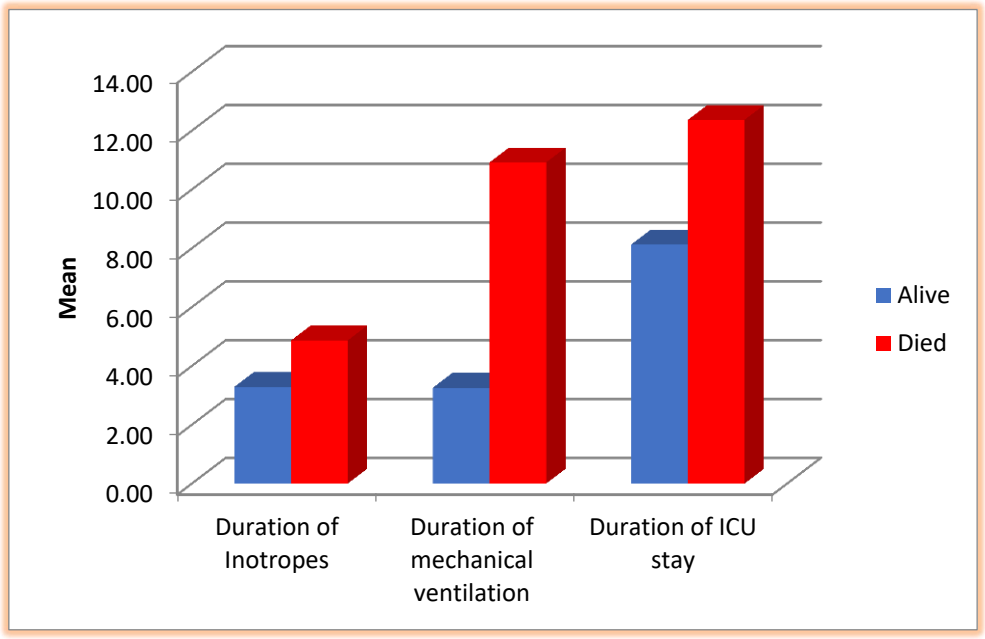
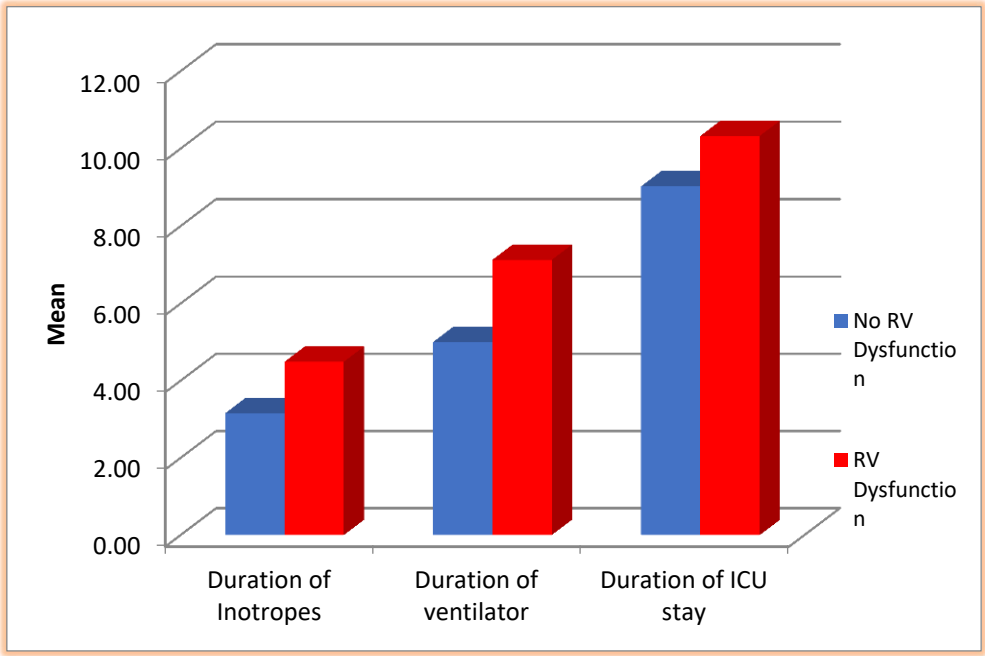


Figure 25: Duration of vasopressors, mechanical ventilation and ICU in RV dysfunction.



RV dysfunction with outcomes.

Table 5: RV dysfunction and AKI

		No RV Dysfunction	RV Dysfunction	Total	Chi-square value	p-value
AKI	No	25(55.6%)	15(27.3%)	40	8.249	0.007*
	Yes	20(44.4%)	40(72.7%)	60		
Total		45	55	100		

*statistically significant

RV dysfunction was significantly associated with AKI with p-value - 0.007

Figure 26: RV dysfunction with AKI

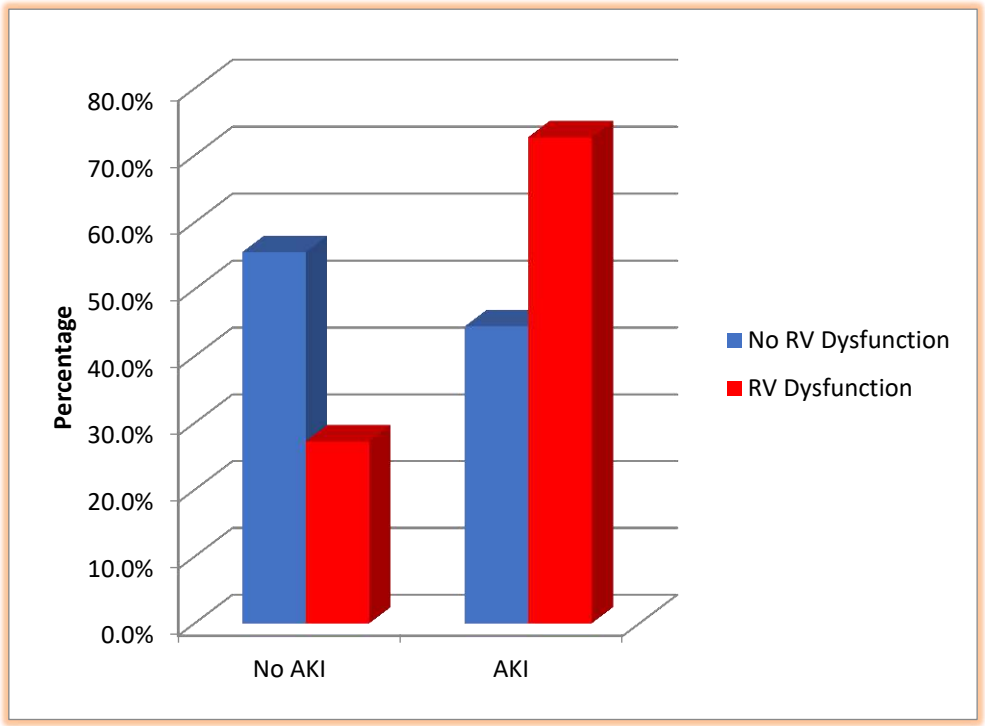


Table 6: RV dysfunction and Mechanical ventilation

		No RV Dysfunction	RV Dysfunction	Total	Chi-square value	p-value
	No MV	21(46.7%)	16(29.1%)	37	3.28	0.096
	MV	24(53.3%)	39(70.9%)	63		
Total		45	55	100		

Not significant

The association between RV dysfunction and mechanical ventilation was not significant. P-0.096

Figure 27: RV dysfunction and Mechanical ventilation

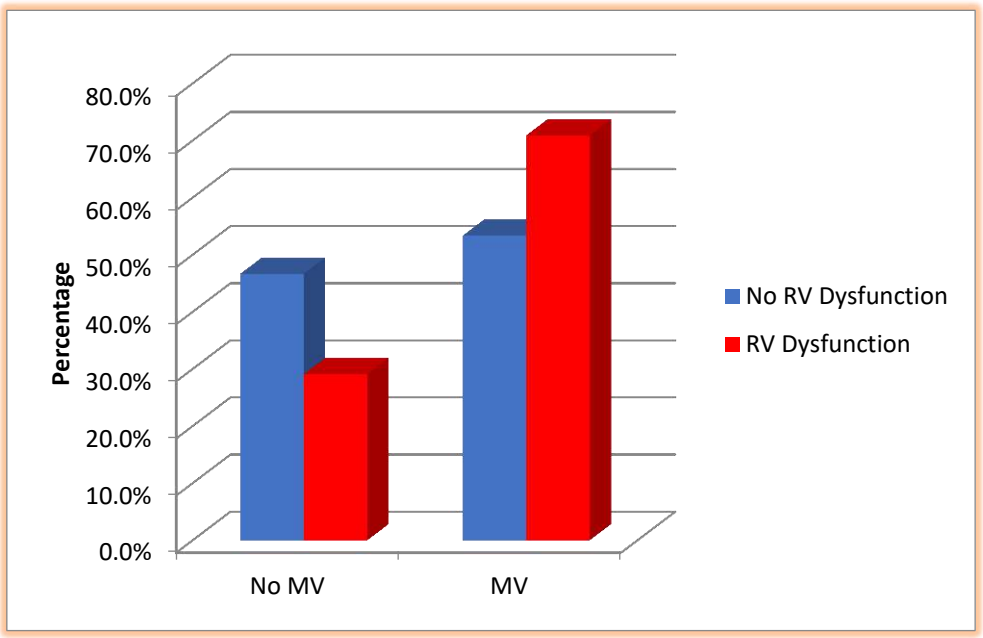


Table 7: RV dysfunction and Mortality

		No RV Dysfunction	RV Dysfunction	Total	Chi-square value	p-value
28 day outcome	Death	12(26.7%)	26(47.3%)	38	4.461	0.035*
	Survivor	33(73.3%)	29(52.7%)	62		
Total		45	55	100		

*statistically significant

RV dysfunction was significantly associated with mortality in septic shock patients.

Figure 28: RV dysfunction with Mortality

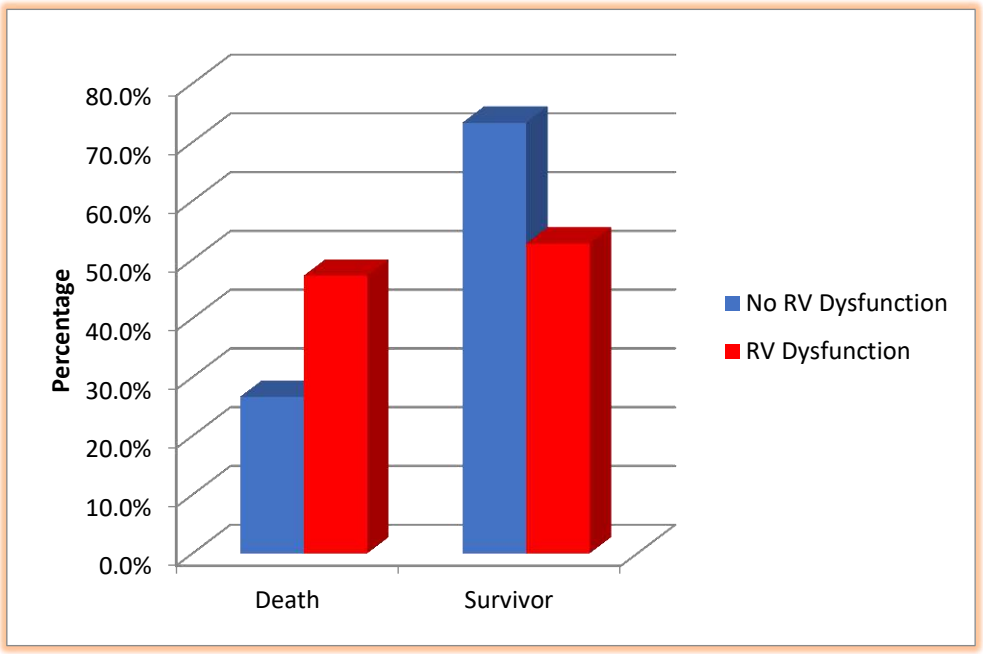


Table 8: Isolated RV dysfunction with mortality

		Others	Isolated RV Dysfunction	Total	Chi-square value	p-value
28 day outcome	Death	23(31.1%)	15(57.7%)	38	5.7831	0.0162*
	Survivor	51(68.9%)	11(42.3%)	62		
Total		74	26	100		

***Statistically significant**

Isolated RV dysfunction (cases without concomitant LV dysfunction or normal echo), also was significantly associated with mortality.

Figure 29: Isolated RV dysfunction with mortality

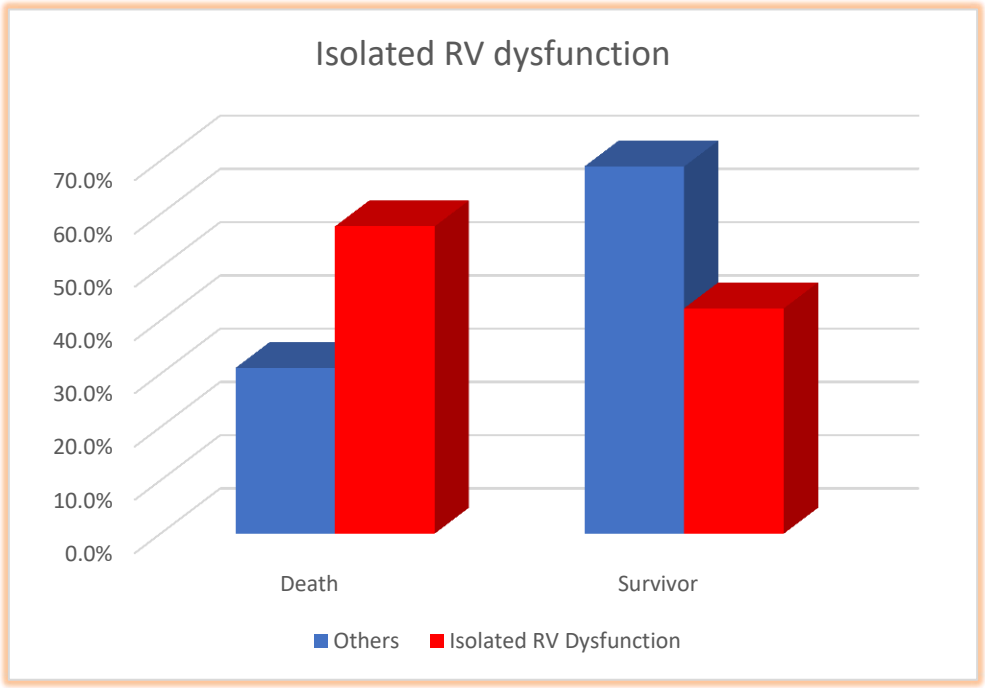


Table 9: Multivariate regression analysis for AKI

AKI	odd ratio	p-value	95% C.I.for odd ratio	
			Lower	Upper
SOFA	1.336	0.001*	1.123	1.589
RV Dysfunction	2.946	0.030*	1.112	7.806
LV Dysfunction	1.026	0.959	0.393	2.678
Duration of Vasopressors	0.941	0.638	0.732	1.211

***Statistically significant**

We conducted multivariate regression analysis for AKI with SOFA score at the time of assessment, presence of RV dysfunction, LV dysfunction and duration of vasopressors of which SOFA score and RV dysfunction turned out be significantly associated with AKI with Odds ratio (OR) of 1.336 and 2.946 respectively.

Table 10: Multivariate regression analysis for mortality

Mortality	odd ratio	p-value	95% C.I.for odd ratio	
			Lower	Upper
SOFA	1.379	0.001*****	1.133	1.678
RV Dysfunction	3.847	0.047*****	1.017	14.552
LV Dysfunction	0.467	0.200	0.146	1.496
Duration of Vasopressors	0.607	0.052	0.366	1.005
Duration of mechanical ventilation	1.321	0.001*****	1.115	1.564

*Statistically significant

Multivariate regression analysis for Mortality was conducted with risk factors SOFA score at the time of assessment, presence of RV dysfunction, LV dysfunction and duration of vasopressors and duration of mechanical ventilation. RV dysfunction, SOFA score and duration of mechanical ventilation were associated with mortality with odds ratios of 3.85, 1.38 and 1.32 respectively.

Table 11: ECHO findings and parameters according to RV dysfunction

	No RV Dysfunction	RV Dysfunction	p-value
RA (cm)	4.01	4.11	0.488
RV basal (cm)	3.96	3.91	0.655
RV mid Cavity (cm)	3.37	3.42	0.700
RV Longitudinal (cm)	7.82	7.82	0.993
TR max (m/s)	176.01	175.65	0.982
PASP (mmhg)	29.94	33.18	0.272
TAPSE (mm)	20.90	17.62	0.001*
RVESA (cm.sq)	11.97	15.30	0.001*
RVEDA (cm.sq)	21.67	22.67	0.287
FAC (%)	44.44	31.81	0.001*
LVEDA (cm.sq)	40.02	34.84	0.001*
LV/RV	0.54	0.65	0.001*
RAP (mmhg)	7.78	12.93	0.001*
LVEDV (ml)	114.72	118.52	0.569
LVESV (ml)	56.60	63.12	0.062
EF (%)	50.02	44.51	0.051
Duration of Inotropes	3.16	4.49	0.001*
Duration of mechanical ventilation	5.00	7.13	0.134
Duration of ICU stay	9.02	10.33	0.316

*Statistically significant

Table 12: ECHO findings and parameters according Mortality

	Alive		Died		p-value
	Mean	SD	Mean	SD	
Age	51.10	15.37	49.29	16.09	0.576
BMI (kg/mt^2)	28.03	4.16	28.73	3.32	0.383
HR	101.10	24.14	109.72	25.00	0.090
MAP (mmhg)	68.05	7.48	68.66	11.60	0.750
SOFA	7.24	2.87	11.05	3.90	0.001*
Lactates (mmol/L)	3.86	2.03	4.37	2.37	0.254
RA (cm)	4.03	0.66	4.12	0.72	0.543
RV basal (cm)	3.90	0.55	4.00	0.57	0.393
RV mid Cavity (cm)	3.41	0.62	3.38	0.52	0.794
RV Longitudinal (cm)	7.79	0.96	7.88	0.90	0.618
TR max (m/s)	178.18	75.91	171.96	77.51	0.694
PASP (mmhg)	30.25	14.14	34.11	15.24	0.201
TAPSE (mm)	19.83	4.95	17.90	4.94	0.062
RVESA (cm.sq)	13.15	2.84	14.86	3.77	0.011*
RVEDA (cm.sq)	21.41	4.27	23.53	4.90	0.025*
FAC (%)	37.97	10.01	36.72	9.80	0.544
LVEDA (cm.sq)	37.55	7.08	36.55	5.58	0.462
LV/RV	0.57	0.07	0.65	0.11	0.001*
RAP (mmhg)	10.02	5.19	11.58	4.55	0.129
LVEDV (ml)	113.43	32.44	122.33	33.48	0.192
LVESV (ml)	61.03	19.08	58.82	14.27	0.540
EF (%)	45.09	14.53	50.08	12.86	0.085
Duration of Inotropes	3.29	1.78	4.87	2.26	0.001
Duration of mechanical ventilation	3.26	5.10	10.92	7.24	0.001
Duration of ICU stay	8.13	5.51	12.37	7.02	0.001

DISCUSSION

Sepsis related organ dysfunction is a well-known entity now. It effects almost all organs of the body including Heart. The overall incidence of septic myocardiopathy ranges from 14- 45%.[49]

Prior studies have largely focused on left ventricular involvement in septic myocardiopathy. But the RV is equally important too.

In endotoxemia and septic shock, the PVR is high due to increased plasma levels proinflammatory mediators, and there is also decrease in contractility, as a part of septic cardiomyopathy itself.

The primary objective of this study was to find the incidence of RV dysfunction in the setting of septic shock and corelate it with AKI, mortality and duration of ICU and mechanical ventilation requirement. Most of the studies available on RV dysfunction in septic shock are retrospective in nature, conducted as a post hoc analysis of other septic shock studies and none of them include Indian population to the best of our knowledge.[40,43,50,51] Assessing differential chamber function of the heart may help in early planning of a management strategy specific for that chamber.

Defining RV dysfunction

Studies have used various cut offs in defining RV dysfunction as evident in the metanalysis by Vallabhajosyula et al.[43] We defined RV dysfunction in this study by the presence of RV dilatation (RV/LV EDA ≥ 0.6) with systemic congestion (RAP ≥ 8 mmHg) or TAPSE < 16mm or RV Functional area change (FAC) <35%. This is in line with the previous major works on RV dysfunction. Lanspa et al[40] in their study defined RV failure with FAC <35% or TAPSE <16mm. Vieillard-Baron et al[39] in their study had RV dilatation (RV/LV EDA ≥ 0.6) with CVP>8 as an indicator of RV failure. Studies have also included visual analysis for identifying RV failure.[41,52]

RV dysfunction in Septic shock

RV dysfunction was frequent (55% of cases) in our study with the definition criteria we followed. This is similar to other studies as well

who have all reported an incidence of 30- 50% depending on definitions.[43] Lanspa et al[40] had an incidence of 48% by screening only with TAPSE and FAC, with similar definition the incidence in our study comes to 48% too. There was no gender preference with RV dysfunction (p- 0.46). Isolated RV dysfunction was present in 26% of the patients with rest of the patients having RV dysfunction had concomitant LV dysfunction. Kim et al[41] reported an incidence of 3.1% isolated RV dysfunction in their retrospective analysis. The higher incidence of RV dysfunction in our study can also be due to higher average BMI (28.29 kg/m^2) in the study population although morbid obese with history of OSA/OHS were excluded from the study. There may be geographical effects like air pollution which is higher in the industrial city of the study and air pollution has been linked to heart dysfunction. Another factor for increased incidence of RV dysfunction in our study population can be the phenotype of sepsis affecting cardiac function.[53]

RV dysfunction in septic shock and AKI

In our study RV dysfunction was significantly associated with AKI in septic shock patients. Overall incidence of AKI was 60%. High incidence of AKI may be due to the fact that only patients who were in septic shock were included. And this being a tertiary care centre generally sick patients arrive with late presentation.

RV dysfunction was associated with AKI , can be explained because systemic congestion, increased capillary filling pressures are known to happen with liberal fluid therapy in the setting of RV dysfunction.[54] Though Lanspa et al[40] do report that renal dysfunction free days were significantly more in patient without RV dysfunction they did not include AKI as an outcome.

Multivariate regression analysis was done for AKI with SOFA, RV dysfunction, LV dysfunction and duration of vasopressors as risk factors. RV dysfunction was significantly associated with AKI with an Odds ratio of 2.94 (1.1- 7.8, 95% CI). Other significant risk factor was SOFA score with an OR of 1.3. Most studies have not included AKI as

an outcome. This may be due to the fact that AKI is very common in sepsis itself. We have kept AKI as an outcome as AKI has been linked to right heart failure.[54]

RV dysfunction in septic shock and Mortality

Overall mortality in the study population was 38%. Again the higher mortality may be attributed to sick patients (mean SOFA at presentation was ~8.7). Mortality in patients with RV dysfunction was 47.3 % which was statistically significant in univariate analysis (p-0.03). RV dysfunction was associated with higher 28 day mortality was independent of LV dysfunction. This is consistent with studies by Lanspa et al[40], Kim et al[41] and Hiraiwa et al[52]. Even isolated RV dysfunction was associated with increased mortality (P<0.0162) as seen with Hiraiwa et al and Vallabhajosyula et al[50] although in the latter study it was long term mortality not short term.

So patients with isolated RV dysfunction or combined RV/LV dysfunction had higher mortality in our study.

Multivariate regression analysis was done for mortality with SOFA, RV dysfunction, LV dysfunction, duration of mechanical ventilation and duration of vasopressors as risk factors. RV dysfunction was significantly associated with mortality with an OR of 3.84 (1.0- 14.5, 95% CI, p- 0.047). Other significant risk factor was SOFA score and duration of mechanical ventilation with an OR of 1.4 and 1.3 each.

RV dysfunction with duration of vasopressors requirement.

The mean duration of vasopressors received overall was 3.89 $\pm$ 2.11 days in our study. When compared with subjects without RV dysfunction (3.16 $\pm$ 1.85 days) , subjects with RV dysfunction had longer requirement of vasopressors of 4.49 $\pm$ 2.13 days which was statistically significant (p- 0.001). Vallabhajosyula et al [50] found similar results in their study. In a very recent trial Bendary et al [55] also found significant increased requirement of vasopressors in RV dysfunction.[55] However Lanspa et al[40] , Vallabhajosyula et al [50] and Kim et al[41] found no difference between vasopressor requirement or doses in

patients of RV dysfunction when compared to those without. It can be related to inclusion of early sepsis patients without septic shock by Lanspa et al , Vallabhajosyula et al [50] however Kim et all did include only septic shock patients.

RV dysfunction with duration of Mechanical ventilation requirement

The mean duration of mechanical ventilation received was 6.17 ± 7.04 days in our study. When compared with subjects without RV dysfunction (5 ± 6.77 days) , subjects with RV dysfunction had longer requirement of mechanical ventilation of 7.13 ± 7.18 days which was however not statistically significant (p- 0.134). The study from Lanspa et al[40] showed significant difference in ventilator free days between the patients. Kim et al[41] also showed increased mechanical ventilation requirement in septic myocardiopathy and not RV dysfunction alone. However Bendary et al[55] found no difference in ventilator duration similar to our study.

RV dysfunction with duration of ICU stay

The mean duration of ICU stay was 9.74 ± 6.44 days in all patients. RV dysfunction patients had slightly higher duration of ICU stay (10.33 ± 6.23 days) compared to those without RV dysfunction (9.0± 6.68 days) but it was not statistically significant (p-0.316). Vallabhajosyula et al [50] also did not find any difference in length of ICU stay with respect to RV dysfunction. Kim et al[41] reported a significantly longer duration of ICU stay but in septic myocardiopathy as a whole, not specific to RV dysfunction.

LV DYSFUNCTION

LV dysfunction was defined as EF < 45% in our study and it was frequently observed with incidence of 42%. Incidence of Isolated LV dysfunction was 13% only whereas incidence of isolated RV dysfunction was higher at 26%. Interestingly enough LV dysfunction

was not associated significantly with AKI or mortality in our study like RV dysfunction.

The disparity in incidence of RV dysfunction compared to LV dysfunction can also be because of the definition of RV dysfunction that we have followed. As indicated in studies LV dysfunction might be an adaptive mechanism in patients with sepsis.[56] RV dysfunction especially if isolated can be difficult to adapt to with ongoing insults like aggressive fluid resuscitation, mechanical ventilation and use of vasopressors and specific management is necessary.

LIMITATIONS OF THE STUDY

- Confounding factors such as various drugs used including fluid resuscitation, vasopressor use, and mechanical ventilation and higher BMI could have all influenced RV dysfunction. Though these things are dynamic in a state like sepsis with lack of clear guidelines in identifying or quantifying RV dysfunction, only TTE findings were taken to identify RV dysfunction.
- Patients without history of prior cardiac or lung disease were included in the study. Though the likelihood of underlying RV dysfunction is low it could have been 'unmasked' following septic shock and hospitalization.
- There can be wide inter as well as intra observer variation in TTE assessment.
- This was a single center study with a small sample size.
- Advanced diagnostic techniques like strain imaging are shown to be better in RV dysfunction in other studies and was not available for bedside evaluation

SUMMARY AND CONCLUSION

This was a prospective observation study conducted in a tertiary care hospital in patients of septic shock admitted in ICU. The main objective was to analyse RV dysfunction in septic shock and its outcomes.

Salient findings

- RV dysfunction was frequent in septic shock with a high incidence of 55% when analyzed using cut offs of TAPSE < 16mm, RV FAC < 35% and RV dilatation with elevated RA pressures.
- RV dysfunction was significantly associated with 28-day mortality, AKI, and duration of inotropes.
- RV dysfunction in septic shock was not significantly associated with duration of mechanical ventilation requirement or duration of ICU stay.
- LV dysfunction was also common with incidence of 42% but it was not significantly associated with mortality or AKI.

Conclusion and Recommendations

- RV dysfunction can be present in more than half of septic shock patients and it is associated with poor outcomes like AKI and mortality.
- LV dysfunction might be an adaptive mechanism in patients with sepsis.[56] RV dysfunction especially if isolated can be difficult to adapt to with ongoing insults like aggressive fluid resuscitation, mechanical ventilation, and use of vasopressors.
- Hence early recognition and specific management of RV dysfunction in sepsis in addition to the sepsis management is crucial.
- Dobutamine in RV dysfunction has shown to improve RV function in cardiac diseases and dobutamine has been indicated as an adjunct to norepinephrine in cases of septic cardiomyopathy as per SSC guidelines.

- Options like specific use of dobutamine in RV dysfunction or early addition of dobutamine to norepinephrine in the management of septic shock need to be explored.
- Furthermore, is fluid management in sepsis is a very high dynamic phenomena and a topic of much debate. So, optimization of fluid management based on non-invasive bed side assessment RV and pulmonary circulation can be significant in preventing systemic congestion and AKI and might add to good outcome.

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S. No	MRD	Age	Gender	Weight	Height	BMI	Comorbidities	Infection source	Mechanical ventilation	SOFA	Lactates	HR	MAP	RA	RV basal	RV mid	RV Longitudinal	TR max	PASP	TAPSE	RVESA	RVEDA	FAC	LVEDA	RV/LV	RV Dilatation	IVC
1	1391967	48	Male	81	1.77	25.9	yes	Lungs	Yes	14	3.3	110	68	4.70	4.55	3.59	7.93	170.0	25.0	25.2	20.00	29.10	31.27	45.50	0.64	Yes	2 < 50%
2	1398742	75	Male	82	1.80	25.3	yes	ST	Yes	15	3.8	131	62	3.48	3.35	3.51	7.15	163.0	26.0	20.0	11.50	25.60	55.08	42.20	0.61	Yes	1.8 cm 40%
3	841089	67	Male	83	1.76	26.8	yes	ST	Yes	9	5.9	99	70	3.67	3.84	2.66	7.71	80.0	23.0	12.0	15.30	23.00	33.48	31.80	0.72	Yes	2 fix
4	1395251	32	Male	84	1.67	30.1	no	Abdomen	Yes	14	2.8	145	66	4.38	4.90	3.67	8.20	70.0	25.0	17.0	18.30	30.60	40.20	37.80	0.81	Yes	2.5 fix
5	131359	62	Female	66	1.67	23.7	yes	Abdomen	Yes	13	9.8	103	88	3.13	3.86	3.30	7.84	149.0	24.0	22.0	17.40	23.50	25.96	36.00	0.65	Yes	1.9 fix
6	1371217	57	Female	67	1.7	23.2	yes	Abdomen	yes	10	15.0	111	86	2.57	3.45	2.66	6.35	55.3	11.0	19.5	12.42	20.20	38.51	37.20	0.54	No	1 >50
7	1356802	63	Female	68	1.66	24.7	yes	Abdomen	no	4	2.6	82	76	2.38	3.25	2.99	6.48	97.6	14.0	18.0	10.90	14.90	26.85	20.80	0.72	Yes	2 < 50%
8	1396171	32	Female	69	1.57	28.0	no	Perpeural	no	5	4.8	125	75	3.04	2.71	2.62	7.28	287.0	60.0	15.0	10.20	18.40	44.57	32.50	0.57	No	2.8 fix
9	1330268	63	Male	85	1.68	30.1	yes	Abdomen	no	4	6.8	132	68	4.21	4.63	4.68	9.25	115.0	15.0	28.0	16.60	27.80	40.29	47.70	0.58	No	1cm 100
10	1370834	58	Male	86	1.66	31.2	yes	Tropical	Yes	21	4.8	96	59	3.84	3.76	3.53	7.51	101.2	22.0	26.0	14.30	25.10	43.03	41.10	0.61	Yes	1.9 ,20
11	1356613	43	Male	87	1.76	28.1	no	ST	no	10	7.8	129	66	3.31	4.45	3.89	8.60	71.6	13.0	31.0	10.50	19.00	44.74	38.00	0.50	No	1.48 40
12	1340154	48	Male	88	1.80	27.2	no	ST	no	6	3.2	145	73	4.28	4.19	3.90	7.60	300.0	41.0	18.0	12.00	19.60	38.78	37.60	0.52	No	1cm 100
13	1328744	45	Female	70	1.58	28.0	no	Abdomen	no	6	5.7	128	67	3.59	3.29	4.56	5.86	235.8	30.2	19.8	9.82	15.70	37.45	30.60	0.51	No	1.8 10%
14	1301122	37	Male	89	1.66	32.3	no	Abdomen	no	3	2.4	98	87	3.56	3.56	2.85	7.41	46.7	11.0	28.0	9.30	17.30	46.24	33.80	0.51	No	1cm >50
15	1356704	70	Female	71	1.56	29.2	no	ST	no	10	3.9	100	62	4.19	3.97	3.62	7.00	125.0	20.0	24.0	14.00	21.20	33.96	39.80	0.53	No	1.6 full
16	1024788	76	Female	72	1.66	26.1	yes	Urinary tract	Yes	12	5.9	95	64	3.50	3.60	2.70	6.80	80.4	11.0	21.0	10.10	17.60	42.61	39.80	0.44	No	1.5 50
17	682797	73	Male	84	1.60	32.8	yes	Abdomen	Yes	8	3.0	101	69	5.20	4.40	3.60	8.33	128.0	24.0	24.0	18.00	25.60	29.69	37.70	0.68	Yes	2.50
18	1299576	72	Male	88	1.65	32.3	yes	Urinary tract	no	7	4.2	104	70	3.29	3.26	2.71	7.72	139.4	15.0	23.0	15.20	17.60	13.64	35.40	0.50	No	2.14 <50%
19	1304232	40	Male	79	1.67	28.3	no	Abdomen	Yes	8	4.6	160	69	3.27	3.32	2.79	6.61	175.5	25.0	16.4	9.20	15.40	40.26	36.50	0.42	No	1.48 >50
20	1297514	24	Male	80	1.81	24.4	no	Lungs	no	7	4.7	93	67	3.30	3.40	3.19	7.60	100.4	23.0	15.0	9.47	15.60	39.29	28.90	0.54	No	1cm 100
21	1308089	60	Female	73	1.7	25.3	no	Abdomen	no	7	3.7	152	69	3.25	3.36	3.10	7.63	134.0	22.0	18.9	12.70	20.70	38.65	38.50	0.54	No	1.84 fixed
22	1308082	44	Male	81	1.82	24.5	no	Abdomen	Yes	11	3.8	91	68	3.36	3.02	2.18	5.90	129.8	13.0	13.5	12.47	15.70	20.57	28.90	0.54	No	0.77 100
23	1301122	37	Male	82	1.76	26.5	no	Lungs	Yes	9	3.7	132	68	4.60	4.80	3.90	9.10	166.9	56.0	14.8	18.00	25.60	29.69	37.70	0.68	Yes	2.2 fix
24	1301437	37	Female	77	1.56	31.6	no	ST	no	4	2.3	111	68	3.15	2.95	2.21	5.78	194.7	20.0	22.7	11.47	14.60	21.44	25.90	0.56	No	0.44 100
25	1303023	36	Female	73	1.5	32.4	no	Blood	Yes	5	9.0	138	69	4.15	4.20	3.50	6.83	216.0	39.0	19.5	15.90	19.80	19.70	30.70	0.64	Yes	1.96 fix
26	1302405	43	Female	73	1.55	30.4	no	Abdomen	no	5	2.6	158	62	3.60	3.42	3.02	7.01	177.9	30.0	17.0	12.80	16.60	22.89	31.20	0.53	No	1.7 <50 %
27	966548	60	Female	80	1.57	32.5	yes	Lungs	no	5	3.6	112	71	4.30	3.68	3.70	7.13	134.0	30.0	24.6	16.50	18.70	11.76	27.10	0.69	Yes	2.21 fix
28	1288459	62	Male	83	1.76	26.8	yes	Lungs	Yes	11	3.5	111	78	3.15	4.02	3.25	8.11	266.8	44.0	24.6	13.90	22.70	38.77	43.50	0.52	No	2.2 50%
29	1299609	28	Female	65	1.71	22.2	no	Abdomen	Yes	5	8.8	122	60	3.76	3.27	3.22	6.21	108.0	24.0	13.5	11.77	17.40	32.36	25.10	0.69	Yes	1.75 fixed
30	1282279	42	Male	84	1.83	25.1	yes	ST	Yes	8	13.2	124	71	3.63	4.41	3.54	8.35	161.1	15.0	20.8	12.98	23.90	45.69	38.80	0.62	No	1.32 >50
31	1284940	49	Male	85	1.81	25.9	no	Abdomen	no	7	2.3	102	66	4.18	4.00	2.96	8.63	113.0	23.0	17.8	11.80	23.90	50.63	45.20	0.53	No	2.04 fixed
32	1268915	51	Male	86	1.78	27.1	no	Tropical	Yes	7	2.6	114	68	3.22	3.30	2.72	7.40	149.0	22.0	16.3	10.80	22.00	50.91	42.80	0.51	No	2.15> 50%
33	1279064	54	Male	87	1.67	31.2	no	ST	yes	8	2.4	108	60	4.92	4.71	3.60	6.31	322.0	66.0	30.0	16.40	28.30	42.05	48.70	0.58	No	2.02 fix
34	701798	35	Male	92	1.71	31.5	no	Abdomen	Yes	5	3.3	78	70	4.60	4.12	3.36	7.70	293.3	55.0	15.9	13.40	23.20	42.24	35.90	0.65	Yes	2.4 fix
35	1271032	70	Male	102	1.66	37.0	no	Lungs	no	6	2.0	124	78	3.66	3.61	3.32	9.39	293.0	45.0	23.0	10.89	18.25	40.33	33.30	0.55	No	1cm 100
36	1256941	70	Male	88	1.67	31.6	no	Lungs	Yes	12	3.6	112	58	4.72	4.52	3.96	7.80	286.0	54.0	10.0	17.00	24.20	29.75	30.00	0.81	Yes	2 < 50%
37	1258918	85	Male	72	1.67	25.8	yes	Abdomen	no	4	2.8	88	71	3.93	4.14	3.01	8.38	228.4	40.0	20.8	10.30	16.80	38.69	33.90	0.50	No	0.9 >50%
38	1268774	45	Female	66	1.72	22.3	yes	ST	no	6	2.3	92	68	3.60	3.80	2.97	7.86	293.3	58.0	12.3	12.40	16.80	26.19	37.30	0.45	No	2.2 fixed
39	1271898	44	Male	92	1.66	33.4	yes	Urinary tract	no	5	2.5	95	66	3.96	4.42	3.66	9.66	233.2	36.8	14.1	14.90	25.50	41.57	44.40	0.57	No	2.15 <50%
40	1251161	60	Female	88	1.66	31.9	yes	CNS	Yes	15	4.9	118	82	3.02	3.17	2.90	7.10	259.0	41.0	18.0	11.70	25.60	54.30	34.60	0.74	Yes	1.34 > 50%
41	1232880	30	Male	93	1.72	31.4	no	Abdomen	Yes	15	2.3	102	68	4.94	3.80	4.50	8.90	230.8	26.0	18.5	14.40	23.20	37.93	30.30	0.77	Yes	2 < 50%
42	1235273	42	Male	91	1.70	31.5	yes	Abdomen	Yes	8	2.7	109	64	3.59	2.98	2.83	8.23	80.0	25.0	25.0	22.40	30.60	26.80	44.00	0.70	Yes	2 < 50%
43	1277984	59	Male	90	1.69	31.5	yes	Tropical	no	7	4.5	90	64	4.47	3.63	3.54	7.91	161.0	28.0	21.4	15.00	21.50	30.23	35.40	0.61	Yes	2.2 fix
44	1394332	54	Male	76	1.76	24.5	yes	ST	Yes	11.8	2.3	125	66	4.07	4.39	4.17	8.05	115.0	18.0	18.0	15.70	23.40	32.91	37.70	0.62	Yes	2 < 50%
45	1358236	28	Male	92	1.71	31.5	no	Lungs	Yes	8	3.1	77	98	3.51	3.76	2.60	8.90	61.9	25.0	24.0	12.10	21.80	44.50	40.60	0.54	No	2.4 fix

S. No	MRD	RAP	RV dysfunction 1 (dilatation + RAP >8)	RV dysfunction 2 (FAC)	RV dysfunction 3 (TAPSE)	RV dysfunction (2 or 3) (FAC/TAPSE)	RV Dysfunction (1 or 2 or 3) (FAC/TAPSE/Dilation+rap)	LVEDV	LVESV	EF	LV dysfunction	Biventricular dysfunnction	AKI	Duration of Inotropes	Duration of ventilator	Duration of ICU stay	28 day outcome
1	1391967	15	Yes	Yes	No	Yes	Yes	174.60	55.50	68	No	no	yes	2	1	4	Death
2	1398742	8	no	No	No	no	No	180.70	88.80	51	No	no	yes	1	1	1	Death
3	841089	15	Yes	Yes	yes	Yes	Yes	111.00	62.00	44	yes	yes	yes	2	4	4	Death
4	1395251	15	Yes	No	No	no	Yes	98.30	68.70	30	yes	yes	yes	4	7	7	Death
5	131359	15	Yes	Yes	No	Yes	Yes	125.20	67.50	46	No	no	yes	4	4	7	Survivor
6	1371217	3	no	No	No	no	No	90.00	38.10	58	No	no	yes	2	6	6	Death
7	1356802	15	Yes	Yes	No	Yes	Yes	95.80	55.90	42	yes	yes	No	1	0	2	Survivor
8	1396171	15	no	Yes	yes	Yes	Yes	110.00	93.30	15	yes	yes	yes	2	0	3	Survivor
9	1330268	3	no	No	No	no	No	158.00	67.00	58	No	no	No	4	0	12	Survivor
10	1370834	15	Yes	No	No	no	Yes	174.10	55.00	68	No	no	yes	5	8	8	Death
11	1356613	8	no	No	No	No	No	147.00	63.90	57	No	no	yes	1	0	3	Survivor
12	1340154	3	no	No	No	no	No	96.10	56.00	42	yes	no	No	1	0	3	Survivor
13	1328744	8	no	No	No	no	No	109.00	90.00	17	yes	no	No	4	0	10	Survivor
14	1301122	3	no	No	No	no	No	94.10	42.90	54	No	no	No	2	0	6	Survivor
15	1356704	8	no	No	No	no	No	137.20	56.30	59	No	no	No	1	0	3	Survivor
16	1024788	8	no	No	No	no	No	112.50	47.10	58	No	no	yes	1	2	1	Death
17	682797	15	Yes	Yes	No	Yes	Yes	115.70	61.80	47	No	no	No	3	2	4	Survivor
18	1299576	8	no	Yes	No	Yes	Yes	100.00	63.00	37	yes	yes	yes	2	0	6	Survivor
19	1304232	8	no	No	No	no	No	137.00	52.20	62	No	no	yes	4	10	10	Death
20	1297514	3	no	Yes	yes	Yes	Yes	78.20	33.20	58	No	no	No	3	0	6	Survivor
21	1308089	15	no	No	No	no	No	96.00	72.50	24	yes	no	No	1	0	2	Survivor
22	1308082	3	no	Yes	yes	Yes	Yes	88.20	62.60	29	yes	yes	yes	4	3	10	Survivor
23	1301122	15	Yes	Yes	yes	Yes	Yes	115.00	71.80	38	yes	yes	yes	6	4	10	Death
24	1301437	3	no	Yes	No	Yes	Yes	85.20	59.60	30	yes	yes	No	1	0	4	Survivor
25	1303023	15	Yes	Yes	No	Yes	Yes	109.60	68.40	38	yes	yes	No	1	1	2	Survivor
26	1302405	8	no	Yes	No	Yes	Yes	102.10	70.10	31	yes	yes	No	2	0	4	Survivor
27	966548	15	Yes	Yes	No	Yes	Yes	89.80	51.30	43	yes	yes	yes	4	0	6	Survivor
28	1288459	8	no	No	No	no	No	80.60	52.80	34	yes	no	No	4	6	20	Survivor
29	1299609	8	no	Yes	yes	Yes	Yes	79.70	61.30	23	yes	yes	yes	3	5	8	Death
30	1282279	3	no	No	No	no	No	113.00	50.00	56	No	no	No	2	1	4	Survivor
31	1284940	15	no	No	No	no	No	124.00	58.70	53	No	no	No	2	0	6	Survivor
32	1268915	8	no	No	No	no	No	90.40	35.60	61	No	no	No	6	14	20	Survivor
33	1279064	15	no	No	No	no	No	151.30	68.60	55	No	no	No	8	7	12	Survivor
34	701798	15	Yes	No	yes	Yes	yes	130.00	68.00	48	No	no	No	5	13	16	Death
35	1271032	3	no	No	No	no	No	46.50	19.40	58	No	no	No	2	0	5	Survivor
36	1256941	15	Yes	Yes	yes	Yes	Yes	112.00	48.00	57	No	no	yes	4	4	4	Death
37	1258918	3	no	no	No	no	No	116.50	49.10	58	No	no	No	2	0	5	Survivor
38	1268774	15	no	Yes	yes	Yes	Yes	126.50	98.60	22	yes	yes	yes	2	0	6	Survivor
39	1271898	15	no	No	yes	Yes	Yes	88.70	54.60	38	yes	yes	yes	2	0	4	Survivor
40	1251161	3	no	Yes	No	Yes	Yes	96.00	43.50	55	No	no	yes	7	10	10	Death
41	1232880	15	Yes	No	No	no	Yes	112.00	65.00	42	yes	yes	yes	8	12	16	Survivor
42	1235273	15	Yes	Yes	No	Yes	Yes	231.90	107.00	54	No	no	No	4	10	15	Death
43	1277984	15	no	Yes	No	Yes	Yes	123.60	94.70	23	yes	yes	No	2	0	5	Survivor
44	1394332	15	Yes	Yes	No	Yes	Yes	94.80	45.00	53	No	no	yes	2	3	4	Survivor
45	1358236	15	no	No	No	no	No	143.00	47.80	67	No	no	yes	4	20	20	Death

S. No	MRD	Age	Gender	Weight	Height	BMI	Comorbidities	Infection source	Mechanical ventilation	SOFA	Lactates	HR	MAP	RA	RV basal	RV mid	RV Longitudinal	TR max	PASP	TAPSE	RVESA	RVEDA	FAC	LVEDA	RV/LV	RV Dilatation	IVC
46	460901	66	Female	86	1.66	31.2	yes	Blood	Yes	6	3.5	109	60	3.77	3.89	3.95	8.14	169.5	35.0	6.9	15.70	19.70	20.30	32.10	0.61	Yes	1.95 fixed
47	1288549	62	Male	88	1.64	32.7	yes	Lungs	Yes	20	3.5	116	68	3.15	4.02	3.25	8.11	266.8	41.0	24.6	22.60	29.60	23.65	33.50	0.88	Yes	2 < 50%
48	1269015	80	Female	78	1.73	26.1	yes	Abdomen	Yes	8	4.5	113	58	3.81	3.09	2.51	7.80	204.1	35.5	10.1	14.20	19.70	27.92	29.80	0.66	Yes	2 < 50%
49	1290873	36	Male	79	1.65	29.0	no	Lungs	Yes	5	3.8	64	67	3.64	3.49	2.80	7.46	199.5	39.0	20.2	9.45	16.20	41.67	34.40	0.47	No	1.76 <50%
50	1154708	38	Male	80	1.78	25.2	yes	Lungs	Yes	12	2.8	86	70	3.75	3.64	3.61	8.60	281.3	56.0	12.7	20.80	36.40	42.86	48.20	0.76	Yes	2.02 fix
51	1448506	66	Female	70	1.71	23.9	yes	Urinary tract	Yes	8	3.6	123	64	4.23	4.71	3.74	8.65	164.1	16.0	20.0	12.98	24.90	47.87	41.60	0.60	Yes	1.32 >50
52	1445183	73	Male	81	1.71	27.7	yes	Lungs	Yes	12	5.6	111	70	2.98	3.55	3.19	6.78	100.6	15.0	17.2	10.90	15.90	31.45	21.80	0.73	Yes	2 < 50%
53	1445210	23	Male	82	1.76	26.5	no	Lungs	Yes	12	2.9	122	64	4.81	4.93	4.88	9.55	188.0	59.0	17.2	16.60	28.80	42.36	40.70	0.71	Yes	2 cm <50
54	1440358	24	Female	71	1.68	25.2	no	Abdomen	Yes	14	2.8	111	58	4.88	4.49	4.10	7.90	303.0	42.0	17.2	12.00	20.60	41.75	38.60	0.53	No	1cm 100
55	1429305	48	Male	83	1.76	26.8	yes	Urinary tract	no	10	5.7	74	67	4.19	3.59	4.76	6.16	238.8	31.2	19.0	9.82	16.70	41.20	31.60	0.53	No	1.8 10%
56	365902	48	Male	84	1.80	25.9	yes	Lungs	Yes	9	4.8	127	46	4.16	3.86	3.05	7.71	249.7	59.0	17.2	9.30	18.30	49.18	29.80	0.61	Yes	1cm >50
57	349317	30	Male	85	1.77	27.1	no	ST	Yes	11	2.8	118	78	4.79	4.27	3.82	7.30	128.0	21.0	23.2	14.00	26.20	46.56	44.80	0.58	No	1.6 full
58	458582	54	Female	72	1.57	29.2	yes	Lungs	Yes	11	2.5	113	80	5.80	4.70	3.80	8.63	131.0	25.0	23.2	18.00	26.60	32.33	38.70	0.69	Yes	2.50
59	144297	27	Male	86	1.64	32.0	no	Lungs	Yes	10	3.6	114	90	3.85	3.66	3.30	7.93	137.0	23.0	18.1	12.70	21.70	41.47	29.40	0.74	Yes	1.84 fixed
60	1444595	58	Male	87	1.67	31.2	yes	Lungs	Yes	8	2.6	101	90	3.75	3.25	2.41	6.08	197.7	21.0	21.9	11.47	15.60	26.47	26.90	0.58	No	0.44 100
61	1443241	52	Male	88	1.69	30.8	yes	ST	Yes	9	3.6	94	85	4.20	3.72	3.22	7.31	180.9	31.0	16.2	12.80	17.60	27.27	32.20	0.55	No	1.7 <50 %
62	1424505	19	Male	67	1.71	22.9	no	Lungs	Yes	7	4.1	95	60	3.75	4.32	3.45	8.41	269.8	45.0	23.8	13.90	23.70	41.35	44.50	0.53	No	2.2 50%
63	1424498	45	Male	90	1.74	29.7	yes	Lungs	Yes	8	2.8	118	88	4.78	4.30	3.16	8.93	116.0	24.0	17.0	11.80	24.90	52.61	46.20	0.54	No	2.04 fixed
64	1450577	50	Male	91	1.72	30.8	yes	Lungs	Yes	11	2.9	69	70	3.82	3.60	2.92	7.70	152.0	23.0	16.5	10.80	23.00	53.04	38.30	0.60	Yes	2.15> 50%
65	1450320	66	Male	60	1.81	18.3	yes	Abdomen	Yes	8	2.4	67	71	5.52	5.01	3.80	6.61	325.0	67.0	29.2	16.40	29.30	44.03	49.70	0.59	No	2.02 fix
66	1212740	68	Female	77	1.61	29.7	yes	Urinary tract	Yes	10	6.4	118	58	5.20	4.42	3.56	8.00	316.3	59.0	17.1	13.40	24.20	44.63	36.90	0.66	Yes	2.4 fix
67	1453273	16	Female	87	1.56	35.7	no	Lungs	no	5	3.0	94	70	4.26	3.91	3.52	9.69	296.0	46.0	22.2	10.89	19.25	43.43	34.30	0.56	No	1cm 100
68	1448991	67	Female	73	1.57	29.6	yes	Urinary tract	no	13	3.8	71	62	4.53	4.44	3.21	8.68	231.4	41.0	20.0	10.30	17.80	42.13	34.90	0.51	No	0.9 >50%
69	1447879	51	Male	102	1.76	32.9	yes	ST	no	8	3.2	68	61	4.19	3.28	3.03	8.53	83.0	26.0	24.2	22.40	31.60	29.11	45.00	0.70	Yes	2 < 50%
70	1451849	61	Male	62	1.77	19.8	yes	Lungs	Yes	10	3.4	110	51	4.24	3.79	3.00	7.76	202.5	40.0	19.4	9.45	17.20	45.06	35.40	0.49	No	1.76 <50%
71	1401470	60	Female	57	1.57	23.1	yes	Abdomen	Yes	7	3.3	123	68	5.30	4.85	3.79	8.23	173.0	26.0	24.4	20.00	30.10	33.55	46.50	0.65	Yes	2 < 50%
72	1400776	62	Female	77	1.56	31.6	yes	Urinary tract	no	11	2.2	106	65	4.08	3.65	3.71	7.45	166.0	27.0	19.2	11.50	26.60	56.77	48.20	0.55	No	1.8 cm 40%
73	375369	70	Male	63	1.80	19.4	no	Lungs	no	5	4.7	86	62	4.27	4.14	2.86	8.01	83.0	24.0	18.1	13.40	24.00	44.17	42.60	0.56	No	2 fix
74	1217650	45	Female	88	1.62	33.5	no	Lungs	no	7	2.5	90	68	4.98	5.20	3.87	8.50	73.0	26.0	16.2	18.30	29.60	38.18	53.80	0.55	Yes	2.5 fix
75	1221382	37	Male	64	1.76	20.7	no	Lungs	yes	11	15.0	67	70	3.17	3.75	2.86	6.65	58.3	12.0	18.7	12.42	21.20	41.42	34.20	0.62	Yes	1 >50
76	1207617	43	Female	86	1.6	33.6	no	ST	no	2	3.0	98	58	4.44	4.06	3.73	7.81	104.2	23.0	25.2	14.30	26.10	45.21	42.10	0.62	Yes	1.9 ,20
77	1186117	43	Female	75	1.59	29.7	no	Abdomen	no	5	4.4	101	80	4.10	3.90	2.90	7.10	83.4	12.0	20.2	10.10	18.60	45.70	40.80	0.46	No	1.5 50
78	1212603	37	Female	61	1.66	22.1	no	ST	yes	6	4.9	123	60	3.87	3.62	2.99	6.91	178.5	26.0	16.6	9.20	16.40	43.90	37.50	0.44	No	1.48 >50
79	493101	45	Female	77	1.61	29.7	yes	ST	yes	7	3.7	114	51	5.20	5.10	4.10	9.40	159.9	47.0	13.2	18.00	26.60	32.33	38.70	0.69	Yes	2.2 fix
80	1213334	36	Female	73	1.54	30.8	no	Blood	yes	14	5.9	122	68	4.36	3.57	3.42	6.51	111.0	25.0	12.7	11.77	17.40	32.36	30.10	0.58	No	1.75 fixed
81	1212014	54	Male	85	1.62	32.4	yes	ST	yes	11	3.5	118	71	5.32	4.82	4.16	8.10	289.0	55.0	9.2	17.00	25.20	32.54	31.00	0.81	Yes	2 < 50%
82	1202011	72	Female	64	1.55	26.6	yes	Urinary tract	no	5	4.0	69	70	3.62	3.47	3.10	7.40	262.0	42.0	17.2	11.70	21.60	45.83	44.00	0.49	No	1.34 > 50%
83	1208649	67	Female	65	1.68	23.0	yes	ST	yes	6	4.5	106	67	4.11	4.06	2.80	9.20	64.9	26.0	23.2	12.10	22.80	46.93	41.60	0.55	No	2.4 fix
84	860837	32	Female	83	1.61	32.0	no	Blood	no	6	2.2	69	68	4.37	4.19	4.15	8.44	172.5	36.0	6.1	15.70	20.70	24.15	34.10	0.61	Yes	1.95 fixed
85	1208961	48	Female	87	1.66	31.6	no	ST	yes	20	2.8	127	64	3.75	4.32	3.45	8.41	269.8	42.0	23.8	22.60	30.60	26.14	34.50	0.89	Yes	2 < 50%
86	1202632	60	Female	68	1.66	24.7	yes	Lungs	Yes	10	2.5	102	65	4.41	3.39	2.71	8.10	200.1	36.5	9.3	14.20	20.70	31.40	30.80	0.67	Yes	2 < 50%
87	1207447	48	Male	89	1.68	31.5	yes	Lungs	Yes	9	4.0	105	63	4.35	3.94	3.81	8.90	284.3	57.0	11.9	12.80	23.40	45.30	43.20	0.54	No	2.02 fix
88	1205443	44	Female	93	1.7	32.2	no	Lungs	yes	12	3.3	111	90	3.73	4.16	3.50	8.14	152.0	25.0	21.2	17.40	24.50	28.98	37.00	0.66	Yes	1.8 fix
89	1107364	62	Male	90	1.70	31.1	yes	Lungs	Yes	10	2.6	88	71	3.64	3.01	2.82	7.58	294.7	61.0	14.2	10.20	19.40	47.42	30.50	0.64	Yes	2.8 fix
90	1205382	42	Female	70	1.67	25.1	yes	Blood	no	3	4.9	104	61	3.91	4.75	4.09	8.90	74.6	14.0	30.2	10.50	20.00	47.50	39.00	0.51	No	1.48 40

S. No	MRD	RAP	RV dysfunction 1 (dilatation + RAP >8)	RV dysfunction 2 (FAC)	RV dysfunction 3 (TAPSE)	RV dysfunction (2 or 3) (FAC/TAPSE)	RV Dysfunction (1 or 2 or 3) (FAC/TAPSE/Dilation+rap)	LVEDV	LVESV	EF	LV dysfunction	Biventricular dysfunnction	AKI	Duration of Inotropes	Duration of ventilator	Duration of ICU stay	28 day outcome
46	460901	15	no	Yes	yes	Yes	Yes	138.00	47.30	66	No	no	yes	6	13	13	Death
47	1288549	15	Yes	Yes	No	Yes	Yes	124.30	45.20	64	No	no	yes	8	22	22	Death
48	1269015	15	Yes	Yes	yes	Yes	Yes	80.10	48.10	40	yes	yes	yes	5	30	30	Death
49	1290873	8	no	No	No	no	No	112.30	46.00	59	No	no	No	6	4	10	Survivor
50	1154708	15	no	No	yes	Yes	Yes	185.00	80.30	57	No	no	yes	9	20	20	Death
51	1448506	3	no	No	No	No	No	113.00	50.00	56	No	no	No	2	5	6	Survivor
52	1445183	15	Yes	Yes	No	Yes	Yes	95.80	55.90	42	yes	yes	yes	6	8	16	Survivor
53	1445210	15	Yes	No	No	No	Yes	158.00	67.00	58	No	no	yes	7	12	12	Death
54	1440358	3	no	No	No	No	No	96.10	56.00	42	yes	no	No	4	6	10	Survivor
55	1429305	8	no	No	No	No	No	109.00	90.00	17	yes	no	yes	2	0	6	Survivor
56	365902	3	no	No	No	No	No	94.10	42.90	54	No	no	yes	3	6	8	Death
57	349317	8	no	No	No	No	No	137.20	56.30	59	No	no	yes	5	19	21	Death
58	458582	15	Yes	Yes	No	Yes	Yes	115.70	61.80	47	No	no	no	6	23	23	Death
59	144297	15	Yes	No	No	No	Yes	96.00	72.50	24	yes	yes	yes	8	10	13	Death
60	1444595	3	no	Yes	No	Yes	Yes	85.20	59.60	30	yes	yes	No	7	22	26	Survivor
61	1443241	8	no	Yes	No	Yes	Yes	102.10	70.10	31	yes	yes	yes	8	14	14	Death
62	1424505	8	no	No	No	No	No	80.60	52.80	34	yes	no	yes	6	18	24	Survivor
63	1424498	15	no	No	No	No	No	124.00	58.70	53	No	no	No	8	28	28	Death
64	1450577	8	no	No	No	No	No	90.40	35.60	61	No	no	No	6	16	16	Survivor
65	1450320	15	no	No	No	No	No	151.30	68.60	55	No	no	yes	4	4	6	Survivor
66	1212740	15	Yes	No	yes	Yes	yes	130.00	68.00	48	No	no	yes	6	14	20	Death
67	1453273	3	no	No	No	No	No	46.50	19.40	58	No	no	No	3	6	10	Survivor
68	1448991	3	no	no	No	No	No	116.50	49.10	58	No	no	yes	4	12	16	Death
69	1447879	15	Yes	Yes	No	Yes	Yes	231.90	107.00	54	No	no	No	4	0	10	Survivor
70	1451849	8	no	No	No	No	No	112.30	46.00	59	No	no	yes	6	14	22	Survivor
71	1401470	15	Yes	Yes	No	Yes	Yes	174.60	55.50	68	No	no	yes	4	6	8	Survivor
72	1400776	8	no	No	No	No	No	180.70	88.80	51	No	no	No	4	0	8	Survivor
73	375369	15	no	No	No	No	No	111.00	62.00	44	yes	no	No	3	0	6	Survivor
74	1217650	15	Yes	No	No	No	Yes	118.30	68.70	42	yes	yes	yes	4	0	7	Survivor
75	1221382	3	no	No	No	No	No	90.00	38.10	58	No	no	yes	2	2	4	Death
76	1207617	15	Yes	No	No	No	Yes	174.10	55.00	68	No	no	No	3	0	6	Survivor
77	1186117	8	no	No	No	No	No	112.50	47.10	58	No	no	No	2	0	4	Survivor
78	1212603	8	no	No	No	No	No	137.00	52.20	62	No	no	yes	1	4	8	Death
79	493101	15	Yes	Yes	yes	Yes	Yes	115.00	71.80	38	yes	yes	No	3	5	7	Death
80	1213334	8	no	Yes	yes	Yes	Yes	79.70	61.30	23	yes	yes	yes	6	8	14	Death
81	1212014	15	Yes	Yes	yes	Yes	Yes	112.00	48.00	57	No	no	No	7	9	11	Death
82	1202011	3	no	No	No	No	No	96.00	43.50	55	No	no	yes	2	0	4	Survivor
83	1208649	15	no	No	No	No	No	143.00	47.80	67	No	no	yes	2	4	5	Survivor
84	860837	15	Yes	Yes	yes	Yes	Yes	138.00	47.30	66	No	no	yes	3	0	8	Survivor
85	1208961	15	Yes	Yes	No	Yes	Yes	124.30	45.20	64	No	no	yes	6	14	10	Death
86	1202632	15	Yes	Yes	yes	Yes	Yes	80.10	48.10	40	yes	yes	yes	5	7	10	Survivor
87	1207447	15	no	No	yes	Yes	Yes	185.00	80.30	57	No	no	yes	3	8	12	Survivor
88	1205443	15	Yes	Yes	No	Yes	Yes	125.20	67.50	46	No	no	yes	7	12	14	Death
89	1107364	15	no	No	yes	Yes	Yes	110.00	93.30	15	yes	yes	yes	6	8	11	Survivor
90	1205382	8	no	No	No	No	No	147.00	63.90	57	No	no	yes	2	0	3	Survivor

S. No	MRD	Age	Gender	Weight	Height	BMI	Comorbidities	Infection source	Mechanical ventilation	SOFA	Lactates	HR	MAP	RA	RV basal	RV mid	RV Longitudinal	TR max	PASP	TAPSE	RVESA	RVEDA	FAC	LVEDA	RV/LV	RV Dilatation	IVC
91	1203117	35	Male	92	1.68	32.6	no	Lungs	yes	16	3.5	110	58	3.89	3.56	2.91	8.02	142.4	16.0	22.2	15.20	18.60	18.28	36.40	0.51	No	2.14 <50%
92	1202116	28	Female	71	1.54	29.9	no	Lungs	no	6	2.7	79	62	3.90	3.70	3.39	7.90	103.4	24.0	14.2	9.47	16.60	42.95	29.90	0.56	No	1cm 100
93	1195899	66	Female	72	1.57	29.2	yes	Blood	no	4	3.4	96	88	3.96	3.32	2.38	6.20	132.8	14.0	18.0	12.47	23.10	46.02	39.90	0.58	No	0.77 100
94	1202572	24	Female	73	1.59	28.9	no	Lungs	Yes	9	7.0	79	61	4.75	4.50	3.70	7.13	219.0	40.0	18.7	15.90	20.80	23.56	31.70	0.66	Yes	1.96 fix
95	1200128	44	Male	98	1.74	32.4	yes	Urinary tract	yes	9	3.6	118	65	4.90	3.98	3.90	7.43	137.0	31.0	23.8	16.50	19.70	16.24	28.10	0.70	Yes	2.21 fix
96	1300804	60	Female	52	1.61	20.1	no	Lungs	no	4	2.5	123	64	4.20	4.10	3.17	8.16	159.7	35.0	17.0	12.40	27.80	55.40	48.30	0.58	No	2.2 fixed
97	1200156	80	Female	75	1.64	27.9	yes	Blood	yes	10	5.9	123	61	4.56	4.72	3.86	9.96	286.2	59.8	17.0	14.90	27.50	45.82	44.40	0.62	Yes	2.15 <50%
98	1199754	38	Male	70	1.68	24.8	yes	Lungs	Yes	8	3.7	74	58	5.54	4.10	4.70	9.20	233.8	27.0	17.7	14.40	24.20	40.50	41.30	0.59	No	1.63 >50%
99	1199714	59	Male	78	1.70	27.0	yes	Tropical	no	8	2.8	98	60	5.07	3.93	3.74	8.21	164.0	29.0	20.6	15.00	25.70	41.63	46.40	0.55	No	2.2 fix
100	1200286	62	Female	76	1.62	29.0	yes	Abdomen	no	6	2.6	88	62	4.67	4.69	4.37	8.35	118.0	19.0	17.2	15.70	23.40	32.91	38.70	0.60	Yes	*1.9 < 50%*

S. No	MRD	RAP	RV dysfunction 1 (dilatation + RAP >8)	RV dysfunction 2 (FAC)	RV dysfunction 3 (TAPSE)	RV dysfunction (2 or 3) (FAC/TAPSE)	RV Dysfunction (1 or 2 or 3) (FAC/TAPSE/Dilation+rap)	LVEDV	LVESV	EF	LV dysfunction	Biventricular dysfunnction	AKI	Duration of Inotropes	Duration of ventilator	Duration of ICU stay	28 day outcome
91	1203117	8	no	Yes	No	Yes	Yes	100.00	63.00	37	yes	yes	yes	8	13	16	Death
92	1202116	3	no	No	yes	Yes	Yes	78.20	33.70	57	No	no	yes	4	0	6	Survivor
93	1195899	3	no	No	No	No	No	88.20	62.60	29	yes	no	No	2	0	4	Survivor
94	1202572	15	Yes	Yes	No	Yes	Yes	109.60	68.40	38	yes	yes	yes	5	9	14	Survivor
95	1200128	15	Yes	Yes	No	Yes	Yes	89.80	51.30	43	yes	yes	yes	5	14	14	Death
96	1300804	15	no	No	No	No	No	126.50	98.60	22	yes	no	No	3	0	8	Survivor
97	1200156	8	no	No	No	No	No	88.70	54.60	38	yes	no	yes	3	6	8	Death
98	1199754	3	no	No	No	No	No	112.00	65.00	42	yes	no	No	3	4	7	Survivor
99	1199714	15	no	No	No	No	No	123.60	94.70	23	yes	no	yes	2	0	5	Survivor
100	1200286	15	Yes	Yes	No	Yes	Yes	94.80	45.00	53	No	no	yes	3	0	6	Survivor

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No. BFUHS/2K21p-TH/ 1635 Date 29/10/21

The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.10.2021 has approved the plan of thesis of **Jeevan Kumar**, a student of your college for **DM Critical Care Medicine** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Right ventricular dysfunction in septic shock.

Supervisor
Dr. Parshotam Lal Gautam
Prof. & Head,
Dept. of Critical Care Medicine,
DMCH, Ludhiana.

Co-Supervisor

Dr. Bishav Mohan
Prof.,
Dept. of Cardiology,
DMCH, Ludhiana.

Dr. Gunchan Paul
Assoc. Prof.,
Dept. of Critical Care Medicine,
DMCH, Ludhiana.

The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

161. If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.

162. The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.

RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

CRITICAL CARE MEDICINE

OF THE

BABA FARID UNIVERSITY OF HEALTH SCINECES

FARIDKOT

APRIL, 2021

DR JEEVAN KUMAR

DEPARTMENT OF CRITICAL CARE MEDICINE
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK
For the degree of	D.M. CRITICAL CARE MEDICINE
Name of the candidate	Dr. Jeevan Kumar
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Introduction: The most recent revision of the SSC guidelines, gives a single "1-hour bundle" for the management of septic shock with the requirement to initiate fluid resuscitation immediately in all septic shock patients without exception. Patients undergoing resuscitation eventually reach the limit of right ventricular-arterial coupling, which is coupling of RV function to pulmonary circulation. In these patients further fluid administration leads to capillary leak and worsens organ dysfunction.

Aim of Study: To see the incidence of right ventricular dysfunction in septic shock and correlating right ventricular dysfunction with outcomes in septic shock

Materials & Methods: A crossover study shall be conducted on 90 patients admitted in ICU with septic shock as per sepsis-3 guidelines.

Clinical Significance: This study will help us to optimize fluid resuscitation and avoid over resuscitation, related organ damage and mortality.

Keywords: SEPTIC SHOCK, RIGHT VENTRICULAR DYSFUNCTION, SEPTIC CARDIOMYOPATHY, SEPSIS.

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK"** exist in the Department of Critical Care Medicine, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

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DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

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Department	Critical Care Medicine
Topic of Thesis	RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK
Likely date of appearing in PG examination	May/June, 2023
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PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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4	DATE OF ADMISSION TO COURSE	30/12/2020
5	TITLE OF THE TOPIC	RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK

6.0 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR STUDY

Sepsis is a significant critical care issue with exceedingly high mortality.

The management of sepsis has been subject to much study, and there are now international guidelines regarding its optimum treatment. At its core, the recommendations suggest early recognition of the disease, timely support of failing organs and swift control of the underlying infection. In the most recent version of Surviving Sepsis Campaign guidelines, the previously practiced 3- and 6-h bundles have been combined into a single "1-hour bundle" with the requirement to initiate fluid resuscitation of 30 ml/kg of crystalloids within 1 hour in septic shock.[1] If even after initial fluid resuscitation the mean arterial pressure (MAP) does not improve to about 65 mm Hg it is recommended that vasopressors be initiated.[1] Mortality rates in severe sepsis and septic shock have been decreasing. Nonetheless, the risk of death remains significantly high in comparison to other critically ill patients. The risk of death in sepsis is largely dependent on disease severity, and it is related to the number of organs failing in the septic condition. Circulatory compromise is a hallmark of severe sepsis, and even more so in septic shock. The clinical situation can be complicated further by the addition of cardiac dysfunction as a complication of sepsis. A septic organ dysfunction specifically affecting the heart known as septic cardiomyopathy has been identified. The addition of septic cardiac dysfunction increases the risk of death in sepsis. Its characteristics and frequency, as well as its long-term consequences, are among the keenly studied areas in the recent times.

Prior studies have largely focused on left ventricular involvement in septic myocardiopathy. However, there has been greater recognition of right ventricular (RV) involvement in sepsis in the last few years.

In endotoxemia and septic shock, the RV faces two obstacles, an increase in Pulmonary vascular resistance (PVR) due to increased plasma levels of endothelin-1 and proinflammatory cytokines such as interleukin 1-β,

interleukin 6 and tumor necrosis factor α, and a decrease in contractility, as a part of septic cardiomyopathy.[2]

Sepsis is characterised by vasodilation and decreased resistance in systemic circulation, whereas the pulmonary vasculature resistance may increase due to hypoxic vasoconstriction, acute lung injury, hypercarbia, imbalance in endogenous vasodilators and vasoconstrictors, vascular microthrombi and mechanical ventilation. Fluid administration in sepsis management, further increases the RV preload, which in the setting of elevated afterload compensates by further increasing end diastolic volume and pressure, leading to isolated RV dysfunction.[3] Lack of specific resuscitation strategies in RV dysfunction may lead to its failure. Furthermore, RV dysfunction is associated with false-positive fluid responsiveness, wherein changes in left ventricular outflow parameters or its surrogate with respiratory variation are used to determine fluid responsiveness.[4] In these patients, further fluid administration leads to venous congestion, capillary leak and worsens organ dysfunction.

There is a crucial need to understand RV dysfunction in sepsis and the causative mechanisms associated with higher mortality in this population, which will significantly influence how we prevent and manage this disease process. Thus, we propose to study the incidence of RV dysfunction in sepsis and corelating right ventricular dysfunction with outcomes in sepsis.

6.2 REVIEW OF LITERATURE

Sepsis is a life-threatening complication in response to infection causing end-stage organ dysfunction and death. The word sepsis is derived from Greek term “sepo” which means “make rotten” or “decomposition”. The term was first described by Hippocrates in 400 BCE to describe the process through which infected wounds become purulent. Although the term sepsis dated old, it took over more than 2000 years to understand the pathophysiology of sepsis. Despite advancements in the understanding of the clinical syndrome, hemodynamic monitoring devices and treatment modalities, sepsis is still one of the leading causes of mortality in ICU patients.[5]

The global burden of sepsis is difficult to ascertain, although a recent scientific publication estimated that in 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths. Approximately 85.0% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries. According to the study, the sepsis death rate was 213 per 100,000 people in India, making it the second highest death rate in south asia.[6]

Definitions:

Sepsis 3 (2016): “Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection”.

Clinical criteria for sepsis: Suspected or documented infection and an acute increase of ≥2 SOFA points.[5]

The task force considered that positive qSOFA (quick SOFA) criteria should also prompt consideration of possible infection in patients not previously recognized as infected.[5]

qSOFA criteria:

Altered mental status (GCS score <15)

Systolic blood pressure <100 mm Hg

Respiratory rate >22 breaths per min

Septic shock is defined as subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.[1]

Septic shock can be identified with a clinical construct of sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP ≥65 mm Hg and lactate >2 mmol/L despite adequate fluid resuscitation.[1]

The paramount importance in the management of patients with sepsis and septic shock is that it is a medical emergency requiring assessment and management on urgent basis. This led to the further modification of the SSC 2016 guidelines with an update in 2018. The elements of SSC bundle 2018 are given in Table 1[1]

Table 1: HOUR-1 BUNDLE
1. Measure lactate level. Remeasure if initial lactate is >2mmol/L.
2. Obtain blood cultures prior to administration of antibiotics.
3. Administer broad-spectrum antibiotics.
4. Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
5. Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

Fluid resuscitation is the mostly done without any cardiac evaluation in the initial stages of shock which is presumed to be due to sepsis. Over resuscitation with fluid in non-responders is detrimental. Positive fluid balance is associated with increased morbidity and mortality in multiple studies which show worse overall mortality in critically ill patients, and increased mortality in patients with acute kidney injury, as well as prolonged recovery in patients with acute lung injury/acute respiratory distress syndrome (FACTT trial). Increased mortality in septic shock patients (VASST trial) It is also associated with intra-abdominal hypertension.[7]

Increasing fluid overload induces a vicious cycle of interstitial oedema and organ dysfunction. There is now indisputable evidence that volume overload results in multi-organ dysfunction with adverse patient outcomes.[8] The increased venous pressure has profound effects on microcirculatory flow and organ function. The kidney is particularly vulnerable to increased venous pressure, which leads to increased renal subscapular pressure and reduced renal blood flow. In addition, increased renal interstitial pressure may collapse intrarenal collecting lymphatics compromising lymphatic flow. These effects result in oliguria with a marked decrease in renal function.[9]

But bedside fluid assessment and administration of fluids is mostly guided dynamic indices. Not all the patients who are labelled fluid responders by bedside tests will respond to volume expansion. This false-positive fluid response from these tests could be due to an underlying cardiac dysfunction.[4,10]

Myocardial dysfunction in Sepsis

Cardiac dysfunction in sepsis, also known as “septic cardiomyopathy (SCM)” is common and associated with increased mortality.[11] When severe, SCM may contribute to a cascade of interdependent organ failure. Early studies of SCM pathophysiology focused primarily on systolic and diastolic dysfunction of the LV, but increasing attention to the right side has revealed that the RV may play an important and possibly independent role in SCM and its downstream effects.[12] While the RV has less muscle mass than the left, the two ventricles are connected both in series and via a common septum leading to ventricular interdependence.[13] Under normal conditions, the RV matches the LV cardiac output to maintain left sided filling and forward flow. During sepsis, the combination of increased RV afterload, decreased RV filling with or without poor contractility may hamper the RV ability to keep up with the LV.[12]

Historically, cardiac function in sepsis has been assessed primarily by left ventricular ejection fraction (LVEF). However, LVEF is highly load

dependent and therefore less reliable in assessment of cardiac function in states of low preload or low afterload[14] as in septic shock. Assessing RV function can be considered to identify true non-responders to fluid response.[4]

Several parameters like RV dimensions, Tricuspid annular plane systolic excursion (TAPSE), RV functional area change (FAC), LV and RV end diastolic area (EDA) are used as markers of RV dysfunction.

Antoine Vieillard-Baron et al[15] in their retrospective study included 280 patients with septic shock were analyzed. RV failure was defined as RV dilatation and a CVP≥8 mmHg. 41% of patients had no RV abnormality, 17% had RV dilatation without failure and 42% in RV failure. Higher RV size was associated with a lower response to passive leg raising for a given PPV. TAPSE was found to be overlapping in all the subjects and was not specific to RV failure. 63.5% of patients with RV failure had a normal TAPSE.

In a secondary analysis Michael J. Lanspa et al[16] studied echocardiographic parameters on 393 critically ill patients with severe sepsis or septic shock within the first 24 hours of ICU admission. They defined RV dysfunction as FAC < 35% or TAPSE < 1.6 cm. Patients with RV dysfunction (48%) had higher 28-day mortality (31% vs 16%, p = 0.001). They concluded that RV dysfunction was associated with increased mortality while LV systolic dysfunction was not.

In another retrospective cohort study[17] using a prospective registry of septic shock from January 2011 and April 2017, of 778 septic shock patients who underwent echocardiography, 270 (34.7%) showed SCM. Among them, 67.3% had LV systolic dysfunction, 40.7% had RV dysfunction and 39.3% had LV diastolic dysfunction. LV dysfunction was common but Multivariate analysis showed that isolated RV dysfunction was an independent risk factor of 28-day mortality (OR 2.26, 95% CI 1.04 to 4.91).

Winkelhorst JC et al [18] conducted a Single-centre retrospective cohort study in adult patients admitted to the ICU with severe sepsis and septic shock. RVEF was recorded as an average over the first 24 h. Patients were separated into subgroups according to their RVEF: RVEF less than 20% (A), RVEF 20% to 30% (B), and RVEF more than 30% (C). The primary endpoint was 1-year all-cause mortality. RVEF was independently associated with 1-year all-cause mortality in a highly selected group of patients with severe sepsis and septic shock.

A Meta-analysis of 1,373 Patients Vallabhajosyula S et al [19] reviewed the published literature from January 1999 to April 2020 for studies evaluating adult patients with sepsis and septic shock. Study definition of RV dysfunction was used to classify patients. The primary outcome was all-cause mortality divided into short-term mortality (ICU stay, hospital stay, or mortality ≤30 days) and long-term mortality (>30 days). In this meta-analysis of observational studies, RV dysfunction was associated with higher short-term and long-term mortality in sepsis and septic shock.

HYPOTHESIS:

There can be RV dysfunction in septic shock, and it is associated with adverse outcomes like Acute Kidney Injury(AKI) , respiratory failure and mortality .

6.3 AIMS AND OBJECTIVES:

Primary objective:

Incidence of RV dysfunction in septic shock

Secondary objective:

Correlation of RV dysfunction with outcome

- AKI
- Respiratory failure
- Mortality in septic shock.

7.0 MATERIAL AND METHODS:

7.1 SOURCE OF DATA:

Study design: Prospective observational study

Study place: Intensive care units, Dayanand Medical College, Ludhiana

Duration of the Study: August 2021 to April 2023

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA:

- Patients admitted to ICU with shock and requiring norepinephrine to maintain a MAP > 65 mmhg.
- Cause of shock presumed to be due to sepsis, as defined by 2016 Sepsis-3 guidelines.[1]
- Aged 18-70 years

EXCLUSION CRITERIA:

- Known history of any prior cardiac disease.
- Known history of COPD/ILD.
- Inability to obtain clear ECHO images
- Refusal to participate.

STUDY PROTOCOL:

The study will be performed on 100 patients, admitted to ICU with septic shock as defined by sepsis-3 guidelines and meeting the inclusion criteria. Patients will be resuscitated according to SSC guidelines. Patients with septic shock will initially be resuscitated with crystalloids at 30ml/kg. Following initial resuscitation, if the MAP remains less than 65 mm Hg then nor- epinephrine will be used as the first line vasopressor.[1] Nor-epinephrine infusion will be started at a dose of 0.05µg/kg/min and gradually increased to target MAP >65mmhg.

Baseline TTE functional assessment will be done by trained echocardiographers. In the present study RV dysfunction will be defined as any of TAPSE < 1.7 cm, RVESD/LVESD > 0.6, or RV functional area change (FAC) <35%.[20]

Following data will be recorded: Name, Sex, Age, past medical history of any comorbidities, general and systemic examination, hemogram, RFT, Serum electrolytes, LFT, Chest X-ray and SOFA score, Heart Rate, systolic, diastolic, and mean arterial pressures, vasopressors doses, lactate, PPV, CVP and urine output.

TTE will comprise of Left ventricular ejection fraction- LVEF (%), LVOT (cm), LV wall motion assessment, Left ventricular end systolic diameter - LVESD (mm), Right ventricular end systolic diameter RVESD (mm), RA (mm), RV (mm), RVEDV, RVESV, TAPSE (mm), TRmax (m/s), IVC (cm) and compressibility (%)

FAC will be calculated as (RVEDV-RVESV) *100/RVEDV.

PASP = $4(TRmax)^2$ + CVP

RV/LV ratio will be calculated RVESD/LVESD.

Number of days in ICU , hospital, ventilator requirement if any, AKI and 21 day mortality will be followed up and corelated with RV dysfunction.

No of patients: The sample size is 100 patients.

OUTCOME:

Identifying RV failure in sepsis.

STATISTICAL ANALYSIS

Prevalence of septic shock admitted in ICU was as 6.2 %.[21]

Based on this, sample size (n) was calculated using formula

$n = z^2 * p * (1 - p) / e^2$

$z = 1.96$, $p = 0.062$, $e = 0.05$

$n \approx 90$ patients needed.

100 patients will be included in the study to increase the power of the study. Two tailed ‘t’ test for paired and unpaired data will be used to assess changes between groups. Partial correlation test by Pearson’s method will be used to assess univariate relations. The association between analyzed variables and outcome will be established by using Cox proportional hazard. Results will be expressed as hazard ratios with 95% confidence intervals. A two tailed probability value (p value) less than

0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO,PLEASE DESCRIBE BRIEFLY.

Use of transthoracic echocardiography for LV and RV function assessment, ABG for blood gases and renal function tests.

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached Herewith

8.0 LIST OF REFERENCES

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PROFORMA

S. NO. NAME: MRD: Date:

AGE/SEX:

Comorbidities- DM/HTN

Baseline ABG-

SOFA score-

- P/F ratio-
- Platelet count-
- Bilirubin
- Vasopressors on flow-
- GCS-
- Creatinine-

Mechanical ventilation- Yes/ No

Lactates-

Parameter	**Values**
HR	
SBP/DBP/MAP	
CVP	
IVC (cm) max/min compressibility/distensibility (%)	____/____ ____%
PPV	
PP change on PLR test	
LVEF (%)-	
LV wall motion- (RWMA/GHK)	
RA (mm)	
RV (mm)(basal/mid)	

Signature of Candidate

Signature of Supervisor i

RVESD (mm)	
LVESD (mm)	
RVEDV	
RVESV	
RV/LV EDA	
FAC (%)	
TAPSE (mm)	
TRmax (m/s)	
PASP	

Others-

Cultures

Chest XRAY

WBC

S. Creatinine

Urea

Potassium

AKI (KDIGO) – YES/ NO

Duration of Ventilator days-

Duration of ICU stay (days)-

28 day outcome - survivor/non survivor

Signature of Candidate

Signature of Supervisor ii

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....
.....am willing to participate in the study **"RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....	.....
Signature of the Witness	Signature of the patient / Legal representative
Name:	Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी/ प्रतिनिधि के हस्ताक्षर /अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"RIGHT VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ / ਪ੍ਰਤੀਨਿਧੀ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ